VOL. 2 FASC. 2

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(Postverlagsort Berlin · 27. 2. 1961)

Die Forschung über die Wirkungen und Wirkungsweisen psychotroper Substanzen hat in den letzten Jahren einen unerhörten Aufschwung genommen. Was vordem nur ein erwünschtes Ziel war, ist zu einer neuen Wissenschaft geworden: Psychopharmakologie. Da eine fruchtbare Analyse und Synthese ihrer Probleme nur durch Zusammenarbeit aller Grundfächer (Pharmakologie, Neurochemie, Neurophysiologie, Neurologie, Psychologie und Psychiatrie) möglich wird, ist die Psychopharmakologie eine verbindende, integrierende Forschungsdisziplin. Die ständig anwachsende Literatur dieses komplexen Arbeitsgebietes ist jedoch bisher zwangsläufig über zahlreiche Zeitschriften verstreut, da es bis heute kein Spezialorgan gab, das sich ausschließlich der Psychopharmakologie widmet. Diesem dringenden Bedürfnis zu begegnen, hat sich eine Gruppe von Vertretern der verschiedenen Arbeitsrichtungen der Psychopharmakologie entschlossen, eine neue Zeitschrift „Psychopharmacologia" zu gründen. In ihr sollen die bedeutenden Fortschritte dieses Arbeitsgebietes durch Veröffentlichung experimenteller und klinischer Originalarbeiten, Übersichten der neuesten Literatur sowie kurzer Originalmitteilungen zusammengefaßt werden.

Recent years have witnessed an unprecedented advance in research on the action and effects of psychotropic drugs, and what, formerly, was just a distant goal, has now evolved into a new branch of science: psychopharmacology. As, however, any fruitful analysis and synthesis of its problems can only be attained with the aid of the complete scale of basic sciences (pharmacology, neurochemistry, neurophysiology, neurology, psychology and psychiatry), psychopharmacology constitutes an integrating discipline of research. Owing to the lack of an organ devoted especially to psychopharmacology, the constantly increasing literature pertaining to this complex field of activity has hitherto of necessity been scattered among various periodicals. In order to overcome this drawback, a group of representatives of the various psychopharmacologic sections have engaged in editing a journal, "Psychopharmacologia", in which the publication of original experimental and clinical papers, reviews of recent literature and short original notices will provide a comprehensive survey of the important progress which is being actually achieved in this field of science.

Ces dernières années ont vu un développement sans précédent dans la recherche des effets et du mode d'action des substances psychotropes sur le «Comportement» et ont fait naître une nouvelle science: la Psychopharmacologie. Comme ces problèmes ne peuvent être résolus que par la collaboration des disciplines de base telles que la pharmacologie, la neurochimie, la neurophysiologie, la psychologie et la psychiatrie, la psychopharmacologie est devenue un champ de recherche de première importance. Cependant la littérature toujours croissante en ce domaine de recherche est forcément disséminée dans de nombreux périodiques, puisqu'il n'existe pas encore de journal exclusivement consacré à la psychopharmacologie. Pour répondre à ce pressant besoin un groupe de représentants des diverses disciplines de la psychopharmacologie s'est mis en devoir de rédiger un nouveau journal dans lequel seraient rassemblés les progrès importants de ce domaine, par la publication d'ouvrages originaux expérimentaux et cliniques, ainsi que des rapports sur des questions actuelles.

Richtlinien für die Mitarbeiter siehe am Schluß des Heftes. — Directions to Authors are given at the end of this number. — Directives destinées aux auteurs, voir à la fin du fascicule.

VOL. 2 FASC. 2

PSYCHOPHARMACOLOGIA

Contents / Inhalt / Table des matières

Reviews · Übersichtsartikel · Revues générales

LINDEMANN, E., and J. M. v. FELSINGER, Drug Effects and Personality Theory 69

Original Investigations · Originalarbeiten · Travaux originaux

HOLMBERG, G., and S. GERSHON, Autonomic and Psychic Effects of Yohimbine Hydrochloride. With 4 Figures in the Text 93

Clinical Reports · Klinische Mitteilungen · Communications cliniques

CLARK, M. L., T. S. RAY, A. PAREDES, J. P. COSTILOE, J. S. CHAPPELL, J. A. HAGANS and S. WOLF, Chlorpromazine in Chronic Schizophrenic Women: I. Experimental Design and Effects at Maximum Point of Treatment. With 12 Figures in the Text 107

Short Communications · Kurze Originalmitteilungen · Communications breves

SULZER, E. S., The Effects of Promazine on MMPI. Performance in the Chronic Psychiatric Patient 137

JANSSEN, P. A. J., The Measurement of Observed Differences between Treated and Untreated Animals Using an Ordinal Scale for Ranking the Degree of Confidence in their Judgement of two Unbiased Observers 141

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Psychopharmacologia

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Drug Effects and Personality Theory

By
ERICH LINDEMANN and JOHN M. v. FELSINGER

(Received November 7, 1960)

The beginning of clinical personality studies by pharmacodynamic methods might be dated from the work of KRAEPELIN, who used a variety of stimulating and intoxicating drugs in attempts to isolate and differentiate psychopathological phenomena. Working in collaboration with NISSL, he hoped to locate certain specific places in the central nervous system which were attacked by the chemicals and thus to develop a neurochemical explanation of altered psychological functioning. His concept of "psychosis in miniature" is at present of considerably more than historical importance: we now speak of "psychosomimetic" drugs.

The therapeutic use of drugs which affect behavioral phenomena was stimulated by the development of "narcoanalysis" during the past twentyfive years. Sodium amytal and pentothal, either alone or in combination with analeptics such as benzedrine or coramine, were shown to reduce dramatically withdrawal in catatonic states and to bring about massive "cathartic" discharge of affect in certain traumatic neuroses. Ether has also been found capable of inducing abreactive states. The capacity of benzedrine to alleviate depressive affects was demonstrated. Pharmacodynamic studies of schizophrenia and affective psychosis have been made with mescaline, marihuana, lysergic acid diethylamide (LSD), and Pervitin, with considerable promise of possible therapeutic implications.

Recent advances in endocrinology have also enriched knowledge of the pharmacodynamics of mental function. Untoward mental symptoms are a not uncommon complication of cortisone and ACTH therapy. In retrospect, this might have been anticipated, in view of the long-recognized occurrence of psychosis as a complication of CUSHING's disease. There is an urgent need for greater insight into the factors that determine whether or not there will be a psychotic reaction as a sequel to the administration of these hormones for physical disease (COBB 1957).

Drug Specific vs. Personality Specific Variables

Investigators adopting a psychodynamic approach to the study of behavior soon found it useful to make certain basic distinctions between those behavioral phenomena which seem to be the result of a specific

drug effect and those related to personality variables. In 1934, MALAMUD and LINDEMANN described certain inferences drawn from a comparison of the reaction of schizophrenic and psychoneurotic patients to the administration of suitable doses of sodium amytal, cocaine, hashish, and mescaline: (a) Each drug undoubtedly has certain characteristic effects, but these are quite closely related to the conditions exhibited by the patients when these specific effects are produced. The changes produced by a given drug will not only be elaborated on in the light of the pre-existing psychic state, but totally new types of reaction may result from such an interrelationship. (b) Another equally important factor is represented by the individual characteristics and background of the person himself. Different individuals, even with the same mental condition, may react differently to any one of the drugs. These differences not only show themselves in the superficial structure of the changes produced but reach down deeper into the personality and determine the levels which these effects may reach.

Individual Variation

As CLARK (1932) has noted, individual variation in drug response is to be expected since "variation may be regarded as one of the fundamental characteristics of living matter." His discussion of the quantitative relation between dosage and action of drugs is particularly pertinent to the difficulties of isolating variables in human response to drugs, in pointing out that in so highly complex a system, simple quantitative relations, as between dosage and drug action, are most probably the function of a large number of variables mutually cancelling out each other.

Such characteristics of the individual as age, sex, weight, body type, excitation-inhibition ratio, etc., have been related to the drug response. MARQUIS et al. (1957) as well as ORTON (1957) note sex differences in the response to tranquillizers finding meprobamate more effective with women than men. SHELDON'S (1942) description of body types and correlated traits ascribes resistance to alcohol and cerebral depressants to the cerebrotonics, while viscerotonics are said to respond well to alcohol with no sense of dizziness, drowsiness, or fatigue, and somatotonics are susceptible to central nervous system depressants. MCDOUGALL (1929) also felt that introverts were more resistant to alcohol than were extroverted personalities.

More recently KORNETSKY and HUMPHRIES (1957) using the Minnesota Multiphasic Personality Inventory reported that subjects with high scores on the "Depression" and "Psychoaesthenia" scales showed maximum subjective changes after chlorpromazine, meperidine, secobarbitone, or lysergic acid diethylamide.

Similarly, an excellent study of the relation of personality variables to susceptibility to Methylpentynol, BARTHOLOMEW and MARLEY (1959), demonstrated a clear correlation between high neuroticism scores (on the Maudsley Personality Inventory MPI) and susceptibility to that alcohol.

Typical and Atypical Reactions

In a study of "typical" and "atypical" reaction to a series of drugs (morphine, heroin, pentobarbital, amphetamine, and placebo) v. FELSINGER et al. (1955) reported differential personality dynamics characterizing the two groups. Subjects with atypical reactions (dysphoric after amphetamine, euphoric after opiates, and dysphoric after pentobarbital) stood out in contrast to the larger group of subjects with typical reactions. They were characterized as (1) immature, dominated by impulsive and egocentric tendencies with inadequate control functions of the personality and socialized habits to balance impulsivity; (2) showing strong but diffuse striving for achievement and prestige beyond their capabilities; (3) having recurrent depressed periods as well as showing more Rorschach signs of depressive tendencies; and (4) constituting the most anxious and hostile members of the subject population.

The fact that the atypical reactors were also placebo reactors is interesting in view of an earlier study by LASAGNA et al. (1954) reporting differential personality characteristics between patients obtaining pain relief from a placebo after major operations and those who could not be thus relieved. The matter of the placebo reactor is of considerable importance since it is frequently an unsuspected quantity in drug reactions. BEECHER (1955), points out that placebos may effect a favorable response at a 15 to 58% rate depending on the situation.

Personality Disturbance and Drug Reaction

The nature of the psychiatric disorder is also related to drug reaction as well as to dose required. LINDEMANN (1934) found distinct differences between schizophrenic and neurotic individuals in their reaction to a series of drugs. KLINE (1956) notes the variation in reserpine requirements for neurotic and psychotic populations and states that the scatter in dosage is greater among neurotic than among psychotics. Psychopathic patients are reported as showing no sleep disturbance even after continued large doses of amphetamine sulfate (HILL 1947). v. FELSINGER et al. (1955) also comment on the minimal reaction of psychopathic personalities to various drugs. They view this in terms of a secondary reaction akin to the psychological defense mechanism of "denial."

In a later study of lysergic acid derivatives (di and mono-ethyl amides) these same investigators reported a high correlation between "maladjustment" and degree of drug reactivity as independently measured by psychologist and pharmacologist respectively. The relationship of the pre-drug personality structure and the type of drug reaction was not as apparent with these two drugs as with the former series of drugs. This finding suggests McFarland's (1952) work on anoxia in which he reported a high correlation in neurotics between symptom formation, including physical collapse, and low level of anoxia which left the normal individual unaffected.

In general, then, there is a broad hypothesis correlating susceptibility to drugs, as well as degree and atypicality of reaction, to abnormality of personality.

Such a general hypothesis seems eminently reasonable and findings supporting it are less surprising than the failure to establish a correlation would have been. Certainly the functional state of an organ like the heart can affect the response of an organism to drugs that act on the heart, and the physiological condition of the kidneys may alter the response to diuretics. Thus we should expect that the state of the central nervous system as reflected in the personality structure may affect the response to drugs acting primarily on the central nervous system.

Primary vs. Secondary Effects

Nevertheless, a question remains: Are the basic effects of a given drug reasonably uniform from person to person, the psychological or subjective reactions constituting either elaboration effects by the psychic state, or reactions of that state to the specific drug effects; or is there a basic difference in the intrinsic effects of the drug from subject to subject?

It is likely that the psychological and subjective effects are not directly determined by the drug but related to the alteration by the drug of such psychic factors as needs, drives, or perceptual processes. These changes then are reacted to by the total personality. Thus, as to the opiates, the gratification of primary needs, such as hunger and sex, and relief of pain, or the reduction of the drive consequent to these needs, is viewed as producing the euphoria.

It is perhaps easier to appreciate the role of psychological dynamics in the secondary drug reactions that sometimes supersede an initial and more expected one. These reactions are most easily understood as the result of the operation of integrative functions of the personality that adjust behavior to an acceptable compromise between internal processes and reality demands, or, stated another way, constitute restitutive efforts on the part of a threatened personality organization to

preserve its integrity or reestablish its equilibrium. Altering the internal components of this balance may create fear or panic, and great efforts may be made to integrate the change in an emotionally acceptable manner.

Applying this approach to the problem of "typical" and "atypical" reactions, the drug reactions are seen as a function of differential personality dynamics. As reported above, the atypical responses were most frequent in the least balanced persons. It is not unreasonable to assume that such a personality structure, already inadequate to deal with stresses, tending to impulsivity and anxiety, and fearing loss of control, may be alarmed by the surge of stimulation and energy associated with amphetamine, which would but add to the tension and further threaten precarious controls. A well-balanced personality structure, on the other hand, could conceivably integrate such stimulation into ongoing activity without disturbance and with pleasant affect. The sedative effect experienced after amphetamine by a few subjects is similarly viewed as a secondary defensive reaction of the specific personalities developed to handle the threatening stimulation, and is thus more of a withdrawal reaction than a sleep process.

In like manner the usual effects of opiates (blunting of reactivity, reduction of urgency to action, interference with associational activity, and lassitude) may constitute a pleasant relief and temporary cessation of tension and struggle for the unbalanced personality. To the balanced personality these same effects may well constitute a useless, confusing, unwanted, and unpleasant interference with normal functioning. Thus euphoria in the former and dysphoria in the latter.

The differential affective reaction of the two personality groups to pentobarbital may be explained similarly. Although both pentobarbital and the opiates sedate, they differ in that the opiates may not cloud consciousness or threaten its loss through sleep. In addition, there are other effects of morphine (reduction of anxiety, e.g.) that appear to differ quantitatively from those of pentobarbital. While sleep is ordinarily accepted with pleasant affect, an anxious or wary person may experience this trend with concern if he thinks the circumstances inappropriate or unusual. The experimental situation was presumably not an anxiety-arousing one, for most subjects, but the threat of impaired alertness or consciousness produced in some atypical subjects secondary defensive reactions and attempts at vigilance.

Explanation of atypical responses to sedative or stimulant drugs are often attributed to release or stimulation of "inhibitory centers." There are clinical observations that certain persons (particularly the aged) respond with excitement to barbiturates, and amphetamine has been used to control and quiet hyperactive children and to sedate children who were hyperactive owing to brain injuries (BRADLEY and

BOWEN 1941). Such reports suggest that certain persons are predisposed to atypical reactions to these drugs, whatever the mechanism. However, one must entertain the possibility that a typical reaction may initially occur in a given person, but this may then provoke secondary (restitutive) reactions that are opposite in nature because the primary drug effects constitute a threat to the personality. The latter view is, of course, similar to the one propounded for the opiates, i.e., that psychological modification of predictable drug effects primarily determined the net described response.

Psychosocial Factors

Not only the person himself but also other external factors are significant variables in producing a given drug reaction. LINDEMANN and CLARK (1952) caution that "Situational factors, both those in the patient's life and those in the immediate situation may significantly alter the prospect that a given response will occur." Animal studies have highlighted the effect of social factors on toxicity levels. CHANCE (1946) reported that amphetamine produced little effect on mice kept separated, but if grouped together, the same dose produced striking effects. Single animals could tolerate a dose considerably higher than animals in a group where mutual activation led to a striking fall in convulsive threshold. The analogy to the use of tranquillizers in a ward setting is tempting where effects are undoubtedly related to the size and structure of the group. SABSKIN and EISEN (1957) suggest a number of social factors related to the drug effects including attitude of the staff towards the treatment, quantity and quality of the ward personnel, physical construction of the nursing unit, number of patients per room, size of unit, and the available recreational space, as well as the type of patient being treated, together with the degree of disturbance on the ward.

Personality Theory

These then are but a few of the numerous studies contributing data relating possible personality variables to the drug response. In addition the literature on effects on mental functions, visual-motor performance and mood represents a formidable accumulation of "facts." However, in terms of the complexity of human behavior, the present need is not only more facts but conceptual frameworks which will permit the ordering of the facts and relate them to the dynamic process determining behavior.

Of the psychological theories of behavior, two types have been most frequently utilized in explanations of drug action-conditioning and psychoanalytic theory.

Conditioning Theory. Conditioned reflex theory and its elaboration into learning theory have been extensively utilized in animal work. A current version, operant conditioning (SKINNER) in particular, is a promising technique for investigating certain psychological mechanisms of drug action.

PAVLOV (1927) early concluded that "constitution" played a basic part in determining the degree of stability of the dynamic equilibrium of excitation and inhibition of the cerebral cortex. Dogs tended to show differing predispositions for developing and retaining "positive" and "negative" CR. Classifying the dogs as "excitable" or "inhibitory" in temperament, he reported differential drug susceptability in these dogs. The "strong excitatory" dogs, which developed stable conditioned salivary responses more easily, required eight times the dose of bromide then did dogs of the same weight, but of a "weak inhibitory" type.

This concept of an excitation-inhibition ratio balance was postulated as underlying the personality differences between "extrovert" and "intovert" in the sense that extroverted behavior patterns are produced by strong reactive inhibition and/or weak excitation, while introverted behavior patterns are produced by weak-reactive inhibition and/or strong excitation.

MCDOUGALL (1929) utilized the idea in stating "... the introvert by reason of the predominant activity of his cortex and in virtue of its restraining or inhibitory effect on the outflow of thalamic excitation in its normal or direct channels of emotional expression is a man in whom thought seems to flourish at the expense of emotion... introversion seems then to be the natural consequence of the great development and free activity of the cortex." He than postulated some internal secretion which antagonized and moderated the inhibiting influence of the cortex and thus determined various degrees of introversion-extroversion. In support of such a hypothesis, he describes the influence of alcohol, ether, and chloroform in diminishing cortical control over lower brain levels and claims that the markedly extroverted personality is very susceptible to the influence of alcohol, in contrast to the introvert who "can take a considerable dose without other effect than that he becomes extroverted... Alcohol in short seems to be an extroverting drug..." Recently this theory has been applied to drug action by EYSENCK (1951, 1957) who reformulates it in terms of "two reasonably well defined groups of drugs whose existence is clearly recognized by pharmacologists and whose contradictory properties are well known" — the central nervous system depressants and central nervous system stimulants (as classified by GOODMAN and GILMAN 1955). He proposes that "Depressant drugs increase cortical inhibition, decrease cortical excitation, and thereby produce extroverted behavior patterns. Stimu-

lant drugs decrease cortical inhibition, increase cortical excitation, and thereby produce introverted behavior patterns." Such a general hypothesis yields predicted relations between drug effects and the various levels of behavior personality theory as indicated:

Drug Effect: Excitant-Depressant.
Causal Level: Excitation-Inhibition.
Clinical-Behavioral Level: Dysthymia-Hysteria.
Test Level: Introversion-Extroversion.

Since conditioning is reported as related to extroversion-introversion in that extroverts condition with difficulty, and introverts condition easily, EYSENCK claims support in the work of FRANKS & TROUTON (1957) who showed that dexedrine increased the rate of conditioning in man while amytal decreased the rate. However, no correlation was found by BARTHOLOMEW et al. (1958) relating susceptibility and conditionability. Again in 1959 BARTHLOMEW and MORLEY studied susceptibility to alcohol (methylpentynol) and its relation to extroversion failing to find the predicted relation.

EYSENCK also claims support in the work of SHAGASS and NEIMAN (1956) who have maintained that extroverted individuals (hysterics and psychopathic personalities) have a low sedation threshold (as measured by electroencephalographic and speech changes to concurrent introvenous injection of amylobarbitone sodium) whereas introverted (dysthymics) subjects have a high threshold. SHAGASS believes that the sedation threshold is an index of anxiety. However, several studies have cast doubt on SHAGASS' conclusions such as PAMPIGLIONE (1958) who found that in only one-third of 58 patients could he demonstrate a definite sedation threshold and concluded that anxiety does not bear "recognizable relationship to the patient's resistance to a sedative..."

Traits vs. Dynamics. Studies such as these then seem to demonstrate the oversimplifica'ion if not futility of attempts to relate *one* personality dimension to drug action or susceptibility.

The inadequacy of such terms as sedation, tranquillizers, stimulation, euphoria, etc., which are commonly used in description of the behavioral effects of drugs has become obvious. To take terms *sedation* and *stimulation* for example, "they may be employed to characterize certain types of behavioral change produced by morphine, pentobarbital, or LSD 25, but they do not convey the subtle, yet demonstrable difference in the effects of these drugs" (WIKLER 1957). Equally, such classification implies an invariability or drug specificity that is not supported by the literature. This is well illustrated by the effect of amphetamine (a "stimulant" drug) and pentobarbital (a "depressant" drug) on normal volunteers (LASAGNA et al. 1955). Measured on scales of "Euphoric-Dysphoric" and "Sedated-Stimulated" (the combination of which would certainly

approximate EYSENCK's introversion-extroversion scale), fourteen out of twenty subjects moved in a Euphoric direction under amphetamine, and 6 moved toward Dysphoria; while after pentobarbital, 9 subjects became euphoric, 8 dysphoric, and 3 showed no reaction. On the Sedated-Stimulated scales, under amphetamine, 9 subjects moved toward sedation, 9 toward stimulation, and 2 showed no change. With pentobarbital, 17 became sedated and 3 stimulated. Similar results were obtained on a mentation "Impaired-Improved" scale. As elsewhere described (v. FELSINGER et al. 1955) these "typical" and "atypical" reactions were related to differential personality characteristics.

It is apparent then that such drug classifications as depressant and stimulant are of limited use at the clinical-behavioral level. The "specificity" of behavioral changes produced by drugs is, as WIKLER (1957) notes, in the nature of "patterns of changes" defined in terms of multiple aspects of behavior, observed under multiple conditions of personal background, present situation, and observer activities.

Work to date makes it appear unlikely even at the biochemical and neurophysical levels, much less the psychological, that one factor or mechanism will be found to mediate drug action in human behavior. It would seem more profitable for research, as in the case of personality study in general, to view drug effects as the function of a dynamic interaction of a number of variables.

New Work in the Psychology of Personality. While psychological theory has by no means produced a comprehensive and unified theory of behavior, the "frames of reference" that have been developed offer promising approaches for the ordering of the facts of drug effects and serve to suggest profitable avenues of approach for research efforts. We now have the benefit of much new work in the psychology of personality and ego development.

Personality theory has been tremendously advanced by the descriptive conceptualizations of ALLPORT & VERNON (1930), by the more dynamically oriented approaches of KLUCKHOHN & MURRAY (1949), MOWRER (1950), and LEWIN (1935), and especially by developments in learning theory as reflected in the studies of DOLLARD (1949) and SEARS (1943). These contributions have led to formulations having in common an emphasis on functional organization rather than on the enumeration of traits and vectors. The workers mentioned agree with the psychoanalytical point of view that personality may usefully be considered as a goal-directed, organized unit in which arrangements are made (a) for the satisfaction of basic drives or tension states, as well as of secondary drives acquired as part of the learning process, through utilization of the proper cues; (b) for the adjustment of needs to opportunities; and (c) for determining the choice of tools for drive

satisfaction in the light of the cultural prescriptions and taboos to which the functioning personality is exposed. Individuals may be distinguished and described in terms of the variety of methods for problem solving at their disposal and the manner in which they habitually solve basic problems of adjustment.

Ego Psychology. This development in personality theory has been paralleled by a considerable growth in ego psychology, both in psychoanalytical studies and in the broader field of experimental psychology. It has become customary to think of the ego as that part of the functioning personality which is the integrative centre of behavior, so far as the personality is well-adjusted and mature. The more mature the person, the stronger is his ego. Its function is to adjust behavior so as to arrive at a suitable compromise between instinctual demands and the world of reality. The perception of the constellation of circumstances in the present has to be related to memories of circumstances in the past in such a way that the behavior pattern can be adapted to the pressure of drives and dissatisfactions demanding attention. At any given moment, efforts at integration are taking place that make it possible to devise a plan of action promising a maximum of drive satisfaction and a minimum of danger and punishment. This process may be more briefly expressed in the following formula: the integrative functions of the ego are designed to provide the proper correlation between its perceptive and its executive functions.

A prerequisite for the study of drug effects, then, is acquaintance with the basic factors that alter the main functions of the ego. Numerous studies in the last decade have shown how strongly memories, perceptions, and anticipations are influenced by motivational factors. ALLPORT and POSTMAN (1947) have studied the distortions such as "levelling" and "sharpening" which occur in pictures as they are successively remembered and described by a series of different reporters. BRUNER & POSTMAN (1947) studied experimentally the effect of anxiety, aggressive drives, and libidinal wishes on perceptual material. Tachistoscopic investigations showed strikingly the differential effects of motivational attitudes upon the perception of written material. RICHARD SOLOMON (personal communication) has demonstrated how the apparent size of token coins shown to children of pre-puberty age undergoes marked distortions depending upon the expectation of what the coin will buy. RAPPAPORT (1950) has reviewed the motivational factors in memory. All these investigators report alterations in the recognition and organization of the raw material that is at the disposal of the perceptual ego. More recent studies on "sensory deprivation" have demonstrated marked distortions in the perceptive field resulting from reduced sensory impact (SOLOMON et al. 1958). Indeed, one might boldly state that an indi-

vidual perceives what he wants to perceive or "what he is looking for," subject to the limitations imposed by a healthy or by an impaired sensory apparatus, as the case may be.

The integrative function of the ego and the particular mode of defence utilized for a tolerable compromise in the choice of action pattern have been studied in relation to the structure of dreams by FRENCH (1938). Much material illustrating the elaboration of phantasies in the solution of adjustment problems has come from the studies of MURRAY et al. (1938) using the thematic apperception test. LEWIN (1935) and DEMBO (1931) have shown how situations of heightened emotional tension, such as anger and frustration, activate special modes of defence to cope with these powerful emotions. Departure from the plane of reality to find solutions in phantasy as well as regression from integrated behavior to primitive forms of aggression illustrate how fluctuations in the strength of drive may alter or impair the integrative functions of the ego.

In addition to all this, the evidence must be considered that the level of integration may be strongly influenced by the over-all state of awareness or consciousness. MILLER (1944) has shown in some detail how the level of awareness, as altered by such factors as fatigue or mechanical injury to the brain, may profoundly alter what is admitted into the integrative process as determinant of action. Moreover, alterations in the level of awareness and correlated changes in integration, the so-called hypnagogic phenomena that take place on going to sleep and on awakening, acquire special significance. Recent studies on the effect of sleep deprivation or prolonged vigil have shown that under these conditions systematic changes occur in mental integration and performance (RIOCH 1959).

In the light of all these factors, the traditional formulation, expressed in terms of personality and situation, may be replaced by a new formulation referring to the goals and motivation of the person, to the methods of defence he employs to guarantee a tolerable balance of emotional pressures, and to the particular form in which he integrates his perceptions, memories, and anticipations for the purpose of organized action. It is also necessary to consider the arsenal of social skills which provides him with tools for alternative solutions of problem situations, and the degree of pressure sufficient to cause him to abandon his customary level of integration in search of a regressive solution.

Such a conception of the person whose functioning it is aimed to alter by the administration of a drug is, of course, equally necessary for the study of the symptomatology that arises spontaneously as part of psychiatric illness. The problems presented for investigation are similar in both cases. Certain outstanding attempts at conceptualiza-

tion, such as the "psychiatric reaction types" described by ADOLF MEYER (1928), and JOHN WHITEHORN's (1953) analysis of the "meaning of symptoms," have made it easier to keep in one frame of reference the drug-induced variations in behavior and the psychopathic changes of spontaneous origin.

Drug Effects and Psychodynamics

In the light of the above discussion, it would seem profitable to relate drug effects to dynamic processes determining personality functioning. Such an approach is as yet only beginning and is beset by many difficulties involved in the operational definition of the concepts. Nevertheless, a beginning has been made, and the few studies reviewed below may illustrate the way in which aspects of contemporary dynamic psychology may lend themselves to the understanding of drug effects on behavior.

The following review is for convenience organized around four concepts—repression, anxiety, drive, and ego functions, which have received the most attention in the literature.

1. Drug Effects on Repression. Most psychoanalytically oriented writers point out the "repressed" quality of much of the verbal and behavioral material following certain drugs and have proposed that a major effect of these drugs is on repressive barriers—acting to weaken them and facilitate release of repressed material.

The action of barbiturates such as pentobarbital, amobarbital, thiopental, and hexobarbital (WIKLER 1957) as well as other drugs such as methamphetamine, ether, carbon dioxide, and mescaline have been explained in these terms. The use of these drugs to produce abreactive states was the basis of the development of "narcoanalysis" as a therapeutic technique. As noted earlier, sodium amytal and pentothal, either alone or in combination with analeptics such as benzedrine or coramine, were shown to dramatically reduce withdrawal in catatonic states and to bring about massive cathartic discharge of affect in certain traumatic neuroses.

In a study of lysergic acid derivatives v. FELSINGER et al. (1956) described "what seems to be a primary psychologic effect of the drug — the exacerbation of existing symptomatology through a weakening of control functions and defense systems." Thus subjects who had paranoid and hostile reactions to lysergic acid diethylamide and lysergic acid ethylamide gave evidence in predrug interviews and Rorschachs of "suspicious attitudes in interpersonal relations." In a similar vein a subject reacting with vivid and erotic hallucinations was described in predrug interviews and Rorschachs as "dominated by sexual fantasies and impulses of a strong homosexual and anal nature." Content mate-

rial of pre- and post-Rorschach illustrate the collapse of controls and breakthrough of usually repressed fantasies.

CATTELL'S (1954) observations of the effects of intravenous injection of mescaline in schizophrenics support this view. Since some of his subjects had been treated by psychoanalysis, he was able to note the rise to consciousness of certain repressed or unconscious impulses following mescaline, although it was not possible to predict which material would appear.

In a more recent report of the drug reaction of schizophrenics to rauwolfia derivatives, AZIMA et al. (1959) concluded that changes were primarily breaks in the defenses of the patients, "an emergence out of the repressed particularly of aggressive impulses, and what appeared to be a shift from paranoid to manic-depressive organization." They also report an increase in dream production in neurotic patients following drug treatment which suggests emergence of repressed materials.

Whether such effects are due to the release of repressed material or merely the effects of the reduction of tension which allows what is ready to come out to appear a little more quickly and perhaps more easily has been questioned by MACKINNON (1948) as well as STROTZKA (1949), and FRANKL and STROTZKA (1949).

WIKLER (1957) also questions the validity of the repressive effects in terms of what he thinks is circular thinking and the a priori assumption of the validity of psychoanalytic theory. He points out that "new material obtained after administration of a given drug is said to have been 'repressed' if by interpretation in accordance with psychoanalytic theory it can be shown to be related 'actually' or 'symbolically' to previous 'unconscious' conflicts which in turn have been inferred by the observer by the same interpretative criteria." Success in predicting the material obtained after drug administration from subjects whose unconscious conflicts have already been determined by pre-drug study would answer this criticism. While no precise study of this nature has been done, the above studies of CATTELL and of v. FELSINGER suggest that this could be demonstrated.

2. Drug Effects on Anxiety. The release of repressed materials as well as any alteration of defense systems such as repression depends in analytic theory on the operation of other variables in personality organization and process. The primary factor in the development of psychiatric symptoms is believed to be anxiety. Essentially, anxiety arises as the result of unresolved conflict between the expression of basic drives as well as secondary drives, and cultural prescriptions and internalized restrictions on their expression. The mechanisms of defense developed by the personality are designed to control the anxiety, and the psychoneuroses are labelled primarily in terms of these mecha-

nisms. Thus the effect of drugs on anxiety has received considerable attention. KUBIE and MARGOLIN (1945) used the analogy of pain reduction by analgesic drugs referring to "psychiatrically analgesic" drugs which function to lower the reaction to unpleasant and painful emotions such as rage, anxiety, or guilt, "thus allowing the patient to explore painful areas of experience without immediate withdrawal at the first warning of discomfort..." Drugs used in narcoanalysis such as thiopental, as well as nitrous oxide, and cannabis are noted in this regard.

The tremendous clinical literature on the tranquillizing agents emphasizes the effectiveness of these drugs on patients showing marked anxiety reactions or those who are extremely restless and tense. It is also noted that such patients during drug treatment show a greater tolerance for situations which were usually anxiety provoking.

The reduction or disappearance of obsessions, compulsions, and other symptoms is thus attributed to the reduction of anxiety by drug action.

It seems significant that among the clinical reports that results with conversion reactions have not been so effective as with other symptoms. This might be predicted from theory since this mechanism tends to more completely control anxiety.

Insofar as delusions and hallucinations in psychotic states represent attempts to control anxiety through alteration of reality, drug reduction of anxiety should alleviate these symptoms. Various clinical studies report the complete reversal of paranoid states, and while most workers do not think that the drugs effect the basic schizophrenic process, the secondary symptoms (BLEULER) are apparently relieved.

In these terms it is not surprising that the drugs that relieve anxiety are rarely effective with depressions that are not accompanied by agitation or psychomotor hyperactivity.

"Tranquillizers" such as reserpine, chlorpromazine, azacyclonol, and meprobamate are most frequently reported as specific anxiety reducers.

That this effect is "specific" to anxiety and not due to an overall sedation, such as produced by the barbiturates, is supported by the absence of impairment of intellectual functions, except in tests in which motivation plays a major role. While morphine also reduces anxiety, it tends to impair perceptual and intellectual functions.

Each drug, however, appears to have its own "pattern specificities." In comparing reserpine with chlorpromazine, both of which allay anxiety, OSTOW and KLINE (1958) believe that reserpine also has an ego-impairing effect which is similar to but not as great as the somnifacient drugs. Reality testing and repressive barriers are impaired by reserpine, but intellectual problem solving and "constructing an internal image of the world" are not.

3. Drive effect. The mediating concept of "drive" has played a particularly important role in both analytic theory and in modern learning theory derivatives of conditioning theory. Its fundamental physical reference is promising to those seeking bridges between behavior and biochemical processes. The functional properties ascribed to drive states or conditions are basically similar whether one is using the concept in the operational sense of hunger, sex, or fatigue drive or in the less specified form of instinct, libido, or psychic energy. The key role of drive in terms of drive reduction or drive increment as reinforcement, the process by which bonds or associations between stimuli or cues and responses are forged, and its extension in the concepts of secondary reinforcement or motivation have provided a framework for the integration of a major portion of human behavior theory.

The function of drive or instinctual forces in the analytic theory of the neuroses and psychoses likewise centers interest in drug effects on drive states since pathological behavior is seen as the result of the piercing of defenses by instinctual forces. Alteration of these forces should result in the modification of the behavior.

Thus one of the main effects of morphine is assumed to be the reduction of primary drives, not only pain, but hunger and sex as well. This effect is seen particularly in cases of morphine and heroin addiction. In the same manner, amphetamine decreases food intake in both animals and man.

Drug effect on "acquired" or secondary drives is also demonstrated in studies where morphine has reduced the anxiety associated with the anticipation of pain (WIKLER 1957), in contrast to pentobarbital which has failed to exert such an effect. Several studies have suggested that drugs may exert "specific" effects on motivations. In further comparison of the effects of morphine and pentobarbital, HILL et al. (1957) demonstrated that depending on the conditions of reward and incentive, the same dose of drug could actually exert no effect, or act as a "stimulant", or as a "depressant" on visual-motor reaction times. "Thus the action of morphine changed from 'stimulant' to 'depressant' when conditions changed from 'low' incentive... to 'high' incentive, whereas the action of pentobarbital changed from 'depressant' to 'stimulant' when identical changes in incentive level were made." Such studies of drug effect on motivations and secondary reinforcements are most promising since they permit the evaluation in man of many hypotheses derived from animal studies utilizing pain, hunger, and sex drives.

The most recent formulation of the effect of drugs on drives has been presented by OSTOW and KLINE (1959) in terms of psychic energy changes which may be viewed both in the framework of psychoanalytic theory or as simply one component of a total "physiologic energy reservoir."

Confirmation of such hypotheses may equally proceed on both levels, i.e., in terms of predictions of outcomes of behavior by drug induced manipulations of drive level and in terms of biochemical and physiological indices of energy levels such as change in levels of ademosine triphosphate or muscle action potentials.

In essence, they propose that the psychodynamic action of both chlorpromazine and reserpine produces a reduction in the intensity or the amount of forces activating instinctual behavior. By this assumption, they try to account for a variety of apparently unrelated changes in behavior which are seen in normal and abnormal individuals after the administration of these drugs. Their argument is the following:

> Clinically, this reduction would become manifest in poverty of initiation of behavior and retardation in the pursuit of instinctual goals. Our thesis would then explain the reduction of psychomotor activity. If the individual is less preoccupied with the single-minded pursuit of his neurotic or psychotic needs, he becomes more susceptible to external influence which is no longer necessarily distracting or frustrating, but which may offer newer, more promising sources of gratification. Accordingly, docility, tractability, and compliance replace indifference, irritability, and intransigence. Agitation, which is a form of psychomotor overactivity, and which often seems to be the patient's way of working off in undifferentiated movements blocked instinctual impulses, is reduced when psychic energy is reduced. The apathy of the normal subject is a direct demonstration of the reduction of psychic energy. The fact that the drugs usually relieve insomnia may be interpreted simply as a consequence of the reduction of pathogenic psychic drive. However, the fact that they facilitate sleep requires the additional assumption (or offers the inference) that sleep supervenes when instinctual drive is attenuated. The fact that the subject who has taken either drug is readily aroused by sensory stimuli indicates that there is no afferent blockade and that a perceived external demand can mobilize instinctual energy which is not forthcoming spontaneously.

This thesis would fit in with the observation that chlorpromazine and reserpine are not sleep inducing like the barbiturates and that they do not impair such ego functions as perception, intellectual operations, and organized activity. It would explain why highly inappropriate behavior, which is the result of pathological defenses against excessive drive, is replaced by more normal behavior and why, under certain circumstances, such as in cases of catalepsy, an increase in activity is seen which contrasts with the reduction in the activity of agitated patients. If neuroses and psychoses represent conditions in which unconscious instinctual drives have broken through the repressive barrier, then a reduction in such drives achieved by the drugs would help to re-establish the effectiveness of these barriers. The threatened or accomplished escape from repression of instinctual residues is considered as the pathogenic situation. Both the reduction of instinctual drives and the strengthening of repressive forces might lead to more integrated behavior. Ostow and Kline (1958) go further and suggest

that the repressive barrier is not affected as such by the drugs because the clinical evidence shows that all activity, including the ego syntonic activity, is affected and that the picture of apathy develops following larger doses of the drugs. It is the *relative* effectiveness of repression which is reinstated, and this improved balance would account for the many varied qualitative changes in behavior which may best be explained by the disappearance of pathological defences and by the reappearance of more normal goal-seeking activity.

A similar formulation would hold for the disintegrating effects which the administration of ACTH and cortisone have on the organization of behavior and experience in certain individuals. Fox and Gifford (1953) believe that the simplest and all-inclusive interpretation of the psychosis-like phenomena seen in such conditions would be to assume that there is an increase in drive energy which disturbs the equilibrium between unconscious drives and motivations on the one hand and the repressive and integrative forces and resources of the ego on the other.

4. Ego Functions. The growth in ego psychology and the greater emphasis placed on ego function in psychoanalytical theory is reflected in the approach of Lindemann (1959) and Lindemann and Clark (1952) who view drug effect in terms of basic factors that alter the main functions of the ego. Changes may be brought about by at least three avenues: (1) The reduction or modification in perceptive cues; (2) modification by sedative action on the preformed mechanisms leading from waking to sleeping or vice versa, and (3) a change in attitudes or state of dis-involvement as if that of a spectator.

The first type of action is best exemplified by the capacity of morphine selectively to reduce the response to physical pain or emotionally unpleasant stimuli, perhaps by preventing the elaboration of their painful implications at an integrative level. Modifications in perception may be illustrated by the marked distortion of the perceived order of the outer world and the body image manifest after administration of mescaline. The person may respond to such perceptual interference by positive or negative integrative efforts. The effect of morphine is usually experienced as pleasure and may take its place as a permanent asset among the pleasure getting devices to be used by the ego for future planning. The distortions in perception following mescaline administration may be exploited for culturally sanctioned elaboration of religious phantasies, as in the use of peyotl in Mexico. On the other hand, however, they may lead to a sense of social isolation because the drug-induced experiences are incompatible with the presumed experiences of others. The ego response may then be great apprehension or may be marked by the features of "depersonalization." In this syndrome, executive functions are abandoned, and the person surrenders

to the role of a passive spectator, becoming affectively neutral and denying all involvement in future planning or action. Or again, the fear of loss of capacity to integrate new experiences into the totality of manageable intrapsychic events may result in great efforts to reformulate in a logically consistent and emotionally acceptable manner the drug-distorted perceptual cues. The subject may believe under mescaline that he has attained new religious insight or developed new philosophies. He seems to manifest excessive efforts to integrate this elusive perceptual material with his habitual cues and anticipations. The needs of the individual in terms of drive satisfaction will tend to make him emphasize certain perceptual changes in preference to others.

Another form of selective change in perceptions can be illustrated by the effect of benzedrine and related compounds. The peculiar reduction in the urgency of basic drives and appetites, as well as of secondary drives such as anxiety and depressive self-punitiveness, suggests a change in the perceptive cues concerning the urgency of drives demanding satisfaction. The person reacts with a capacity to act in a manner promising more remote rewards and is able to make his pleasure-displeasure adjustment at a lower level of immediate satisfaction. The use of benzedrine for weight control is a good illustration. These examples may indicate how even a drug effect having a relatively restricted impact on one area of ego organization may lead to alterations encompassing changes throughout the total structure of the ego.

With this conceptual frame of reference, a second area of drug effects may be considered, in which the level of integration of the ego is modified by a sedative action influencing the performed mechanisms that lead from waking to sleeping and vice versa. Again one may distinguish different types of response. The barbiturates and scopolamine both lead to sleepiness and finally to profound sleep. However, the manner in which the subject passes from full awakeness to profound sleep is strikingly different. After the administration of sodium amytal, one finds a gradual reduction in the critical appraisal of perceptual cues and a diminution in the anticipatory caution with which such are integrated in making plans of action. The critical appraisal of another person's behavior is less apprehensive; past memories, which are usually kept from access to consciousness, are now recalled, and forms of verbal expression that are ordinarily considered inappropriate may be employed in this state of reduced vigilance.

The person may accept this change with the same degree of satisfaction with which sleep is usually greeted if the circumstances are appropriate. However, it is well known to surgeons that under circumstances of heightened anxiety, when extreme vigilance appears to be necessary — for example, before a major surgical operation — the ego

may react with extreme excitement, overactivity, and an aggressive solution of the adjustment problem.

In contrast, under the influence of scopolamine, there appears to be markedly enhanced withdrawal from alert preoccupation with outer experiences and heightened preoccupation with imagery and phantasy, also an ingredient of the going-to-sleep process. This state of revery again may be accepted with satisfaction, or it may lead to increased apprehension.

This shift to preoccupation with imagery and relative neglect of external stimuli is, of course, the most impressive aspect of the effect of substances such as mescaline and LSD, the so-called psychosomimetic drugs. In psychoanalytical language, one could say that they facilitate "narcissistic withdrawal." Instead of leading to a reduction in awareness, as occurs on going to sleep, they increase alertness and cause a vivid concern with new perceptual experiences. The cues available from present perceptions seem to be woven into these elaborations in much the same way as the secondary elaboration of dream material. Instinctual demands have an urgent quality, and at the same time the defensive devices of the ego are utilized in abundance, just as they are during dreaming. Much of this elaboration renders the perceptive world quite unsuitable for planned action and profoundly impairs the executive functions of the ego.

Many of the workers who have studied mescaline intoxication have been puzzled at the peculiar state of inactivity witnessed in subjects given this drug. The attitude is that of an interested spectator whose planned action is waived for the duration of the show. Efforts of the investigator to involve the subject in organized activities, such as participating in experiments, are answered with reluctance or frank refusal. However, a verbal account of the elaborations is given more freely. The curious preoccupation with imagery and its elaboration, combined with the impairment of integrative and executive personality functions, has led many workers to compare these intoxicated states to the spontaneous psychopathology of schizophrenia. From the point of view of psychoanalytical concepts, the differences between drug-induced modifications in personality functions and those of schizophrenic states are much more impressive than the similarities.

The toxic states which we have observed under the influence of both hashish and cocaine again influence the executive functions of the ego, but in quite a different way. Here also dreamlike elaboration of past and present experience is seen, but with it goes a considerable increase in the need to act. Subjects under the influence of cannabis indica were apt to cling to the experimenter, asking to be restrained from sexual assault or from acting upon silly aggressive impulses.

A striking demonstration of shift in executive functions was observed in a study involving combinations of drugs. Combinations of drugs may lead to even greater complexity of adaptive problems for the subject and for the observer. Benzedrine was administered experimentally to a subject under morphine narcosis, who was lying in a markedly euphoric lassitude, preoccupied with erotic phantasies. Shortly after the administration of benzedrine, the subject was observed to become restless and apparently bewildered. He asked the experimenter not to allow him to leave the hospital until fully recovered from the drug intoxication because he was afraid of what he might do. The effect of the benzedrine on the executive functions of the ego appeared to introduce the immiment threat of his acting out his phantasies. This perplexity and apprehension were followed by a depersonalization state with coincident resolution of these distressing feelings.

Discussion

WIKLER concludes his monumental review of The Relation of Psychiatry to Pharmacology (1957) with the statement that "the relation of psychiatry to pharmacology may be epitomized as a joint effort in search for 'pattern specificity' in the actions of drugs, since the existence of such 'specificities,' however complex their patterns may be, implies the existence of 'common denominators' upon which they act, and which are in turn among the variables that determine human behavior." This advice seems well taken and of particular relevancy to the biochemical and neurophysiological aspects of drug response.

However, it seems likely that the search for drug specific patterns of reactions has been confounded by the secondary, restitutive, personality determined reaction. More careful observation and methods are needed to separate the two aspects of the response. From the psychological point of view, we should then emphasize equally the need for careful investigation of "personality specific" reactions to drugs. Indeed as we have noted, there is as yet more evidence of personality-specific reactions to drugs than there is of drug-specific reactions. This might be expected from the functional view of the drug reaction at both the physiological and psychological levels as designed to maintain or regain a characteristic equilibrium or homeostasis that has been disturbed by the drug. Since these restitutive actions are defined and delimited in terms of the personal characteristics of the psychological, as well as the physiological structure we might expect a basic consistency in an individual, not only from administration to administration but from drug to drug. As noted earlier, the latter consistency was found in reactions of college students to morphine, heroin, pentobarbital and amphetamine, and placebo. Different reactions by an individual

to repeated doses of a drug would, by this view, be found to be consistent in terms of changes in a psychological function or condition—such as motivation. This implies the development of the applicability of theories of personality to drug reaction and the description and conceptualization of the drug induced changes in terms of a theoretical model. For analytic theory as we have seen, this may be in terms of the dynamic interplay of forces and defenses. Whatever theory or model used, its validity may be appraised in similar fashion; it should parsimoniously describe known relationships and yield verifiable predictions as to new ones.

Progress here is plagued by difficulties of operational definitions of psychological concepts. Some believe that the primary task in the field is a reformulation of concepts or "intervening variables" into terms that can be defined into sets of unambiguous operations. They are dismayed at the diverse and conflicting results of work utilizing theoretical concepts or different measures of the same variable. Even at the animal level, a drug or class of drugs such as "tranquillizers" has different effects on "experimental neurosis," "conditioned emotional response," "avoidance responses", and "tension", and at present no theory of motivation or general behavior serves to account for these discrepancies.

Such a state of affairs should not be discouraging if we view it as a stage in scientific development characteristic of many areas of knowledge. As MILLER (1956) points out, the development of general principles goes through several cycles or stages. As long as facts are few, a few simple generalizations account for everything. However, as more facts become known the exceptions and contradictions make things seem confused and complex, and simple generalizations fail. This second stage is finally resolved by a radical reorganization developed either dramatically or piecemeal, and the hitherto baffling phenomena are subsumed under a few laws. Finally, this theoretical advance points the way to new experimental paths; new facts are obtained, new exceptions and contradictions found, and the cycle of development is repeated, each cycle, however, representing a firm gain. In psychopharmacology we are most likely in the second stage of this cycle. The simple and inclusive generalizations characterizing most pharmacological texts

i.e. "[Heroin] produces vicious addiction owing to the readiness with which it elicits euphoria" (KRANTZ and CARR 1949)

have given way to a welter of confusing facts emerging from the recent remarkable surge of interest and work in all aspects of the drug response. As we study the results obtained by many behavioral measures and consider the contradictions and complexities derived, we are forced to re-examine the simple generalities and conceptualizations. We are also forced to revamp and probably abandon the common sense cate-

gories based on common words in the language. As noted earlier, such words as sedation, stimulation, euphoria, etc. are clearly inadequate to portray the behavioral changes induced by drugs, and their use implies a fallacious invariability or drug specificity.

This "agonizing reappraisal" is, however, the necessary prelude to the development of new and more comprehensive generalizations of the soon-to-be-hoped-for third stage.

It seems likely, therefore, that progress will be best served by encouraging the diversity of theoretical, methodological, and technical approaches to drug studies that now characterize the field. Premature pressures for "standardization" and comparability of approaches would cut off the very diversity of fact necessary for future progress in theory development and integration.

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Joint Research Project in Schizophrenia and Psychopharmacology,
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Autonomic and Psychic Effects of Yohimbine Hydrochloride

By

GUNNAR HOLMBERG and SAMUEL GERSHON

With 4 Figures in the Text

(Received March 3, 1960)

During the last 20 years various attempts have been made at obtaining reliable tests of autonomic reactivity in mentally ill individuals. Mostly epinephrine and methacholine have been used to induce blood pressure changes, the degree and patterns of which have been claimed to differentiate diagnostic and prognostic categories (MYERSON et al.; LINDEMANN and FINESINGER; FUNKENSTEIN et al. 1950). However, FUNKENSTEIN found the epinephrine test in itself to be without predictive value for the outcome of treatment (FUNKENSTEIN et al. 1952). Other authors have more and more tended to conclude that the methacholine test is only vaguely associated with prognostic factors (SLOANE et al. and LUNDE et al.), and lately most authors have completely failed to find any prognostic value in the test procedures (HOFFER and CALLBECK 1959a; SATTERFIELD; OZTURK et al.; BRAUN and RETTEK; BRILL et al.).

Atropine is another drug which has been used to differentiate groups of mentally ill patients. HOFFER (1954, 1959b) found that schizophrenic cases differed from normal individuals in that they showed a lesser increase or even a decrease in blood pressure in response to this drug. He did not, however, consider the atropine test more accurate than the ordinary diagnostic procedure and thus not of any practical use. It has also been reported that schizophrenics usually give more variable blood pressure reactions to atropine than do normal subjects (DOUGLAS and HOCH).

Barbiturate sedation has been introduced by SHAGASS (1954, 1956) as a tool for determination of the degree of tension and anxiety and for differentation between neurotic and psychotic types of depression. Other authors, however, have found this method of low objectivity (THORPE and BARKER; BRADLEY and JEAVONS) and recently ACKNER (1959) — in spite of all efforts to make the procedure objective and reliable — did not find any significant correlation between test results and anxiety or tension.

In view of the undoubted association between mental disorder and autonomic reactivity a search was made for drugs with adrenergic

blocking properties. Yohimbine hydrochloride (Fig. 1) among others was tried. Yohimbine in fairly high doses in animals exerts adrenolytic effects, and in still higher doses produces sympathetic nerve blockade

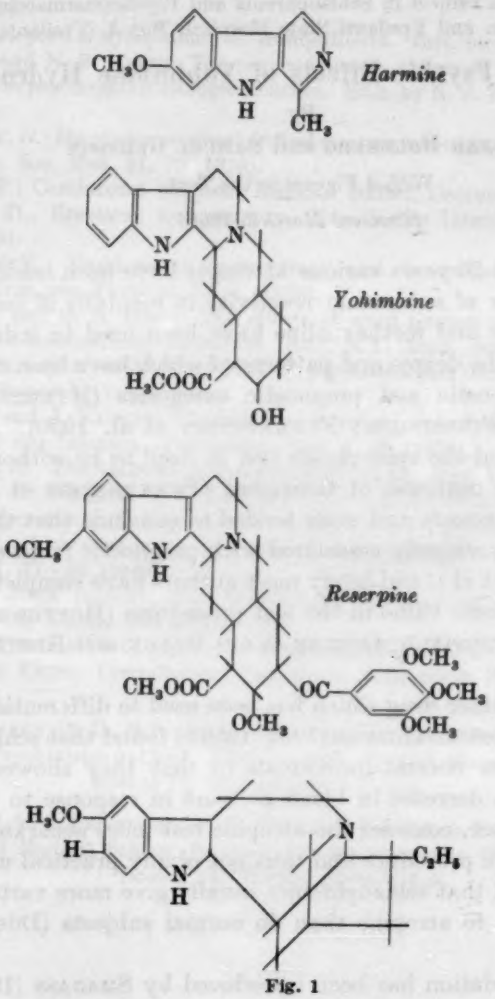

Fig. 1

(Raymond-Hamet; Barry; Yonkman et al.; Bovet and Bovet-Nitti; Nickerson). The central nervous system actions are reported to be less prominent than those of the ergot alkaloids and benzodioxanes. No clinical experiences with yohimbine have been reported, and Goodman and Gilman state that the drug has no proven therapeutic uses. We found this drug to have interesting autonomic and psychic effects which were correlated with the emotional reactivity of the subjects used

(HOLMBERG and GERSHON); and decided that yohimbine warranted more detailed studies to evaluate further its usefulness as a clinical test drug and to investigate its mode of action.

Materials and Methods

A total of 60 cases was studied. Ten cases were used for experiments on modification of epinephrine reaction, seven of which also were used in studies of the preventative effects of sedatives. Three separate groups, of 15 schizophrenic patients, 9 normal volunteers, and 20 mental hospital patients with mixed diagnoses, were used in studies of the relation of yohimbine effects to emotional reactivity. Six further patients were given repeated doses of yohimbine for a study of its psychic effects.

It is considered essential for effective rating that a wide spectrum of patient material be studied, and that the observations be carried out in a stable ward environment for at least three weeks.

For the injection of autonomic drugs we adopted throughout the intravenous route at a constant dose rate. Before each experiment, a heparinized intravenous cannula was inserted and fixed on the arm. Through a rubber membrane on the cannula, injection could later be made as many times as needed without any pain or delay for puncture.

The dose of yohimbine was 0.5 mg/kg, given at an even rate over a period of five minutes. Immediately before the injection a five minute baseline recording was done, and after the injection the effects were observed for at least 15 minutes. During this whole procedure the EKG was recorded continuously and blood pressure taken by auscultation every 30 seconds. In some cases respiration and skin temperature were also recorded and the observation time extended over one hour (see section on direct autonomic effects). The autonomic effects of preparatory procedures (needle insertion and saline injection) were also recorded in connection with the studies of the relationship between yohimbine effects and emotional reactivity.

Emotional reactivity was rated individually by seven skilled raters, using a scale with eight points.

Table 1. *Scale for rating of emotional reactivity*

0	Very little sign of any reactions (more or less stuporous)
1	Definitely (pathologically) sub-reactive
2	Somewhat sub-reactive (the lowest a healthy person could possibly go — many mentally ill people should also fall into this group)
3	Normally reactive (without obvious signs of nervousness)
4	Somewhat over-reactive (a little nervous)
5	Rather over-reactive (quite nervous but not to a definitely pathological degree)
6	Definitely over-reactive (shows abnormal degree of fear and anxiety)
7	Strongly over-reactive (which means that the patient is among the most tense and anxious cases that can be managed in experiments)

The raters were instructed to note especially the reactions of anxiety or fear seen in the subjects during a two-month period of observation. Also the subjects were rank-ordered in the same respect, and the mean ranking list was used for a rank-order correlation (KENDALL) with the autonomic effects of yohimbine. The individual raters were found to be in good agreement, as KENDALL's coefficient of concordance was .827 ($P < .001$).

Results

Direct autonomic effects. The initial response to the injection of yohimbine was facial flushing and an increase in heart rate. Following this, perspiration, salivation, lachrymation, and pupillary dilation were observed, concomitant with a rise in blood pressure. In the more markedly affected cases, nausea and sometimes urgency of micturition and defecation occurred. Erection was observed in 10—20% of the cases, apparently unrelated to other signs and symptoms.

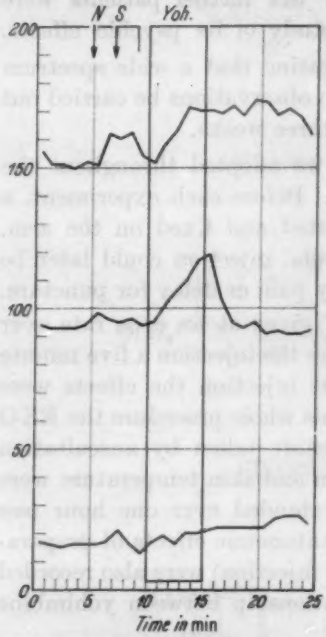

Fig. 2. The effect in one case of preparatory procedures (*N* needle insertion, *S* saline injection) and infusion of yohimbine 0.5 mg/kg (Yoh.) on systolic blood pressure mm Hg (upper curve), heart rate beats/min (middle curve) and respiratory rate/min. (lower curve)

In all our subjects the maximum heart rate increase ranged from 4 to 48 beats per minute. The peak generally was reached during or immediately after the period of yohimbine injection, while return to baseline varied from 3 to over 55 minutes. Those cases that exhibited a less marked rise in heart rate usually showed a secondary drop below baseline.

Systolic blood pressure rose by 2—93 mm. Hg., and this occurred more slowly than the heart rate response. The maxinum increase occurred 5—20 minutes after the injection, and the increase frequently lasted longer than 55 minutes (Fig. 2). Diastolic pressure generally showed a more moderate rise.

The respiratory rate and volume usually increased a little. Hand temperature generally fell, in most cases followed by a secondary rise. Other autonomic signs essentially paralleled the degree of heart rate change.

Modification of epinephrine reaction. In a group of 10 cases, consisting of five schizophrenics, two sociopaths, two alcoholics and one syphilitic chronic brain syndrome, epinephrine tests were performed

Table 2

	Epinephrine alone			Epinephrine after yohimbine		
	Baseline	Epi-nephrine	Difference	Baseline	Epi-nephrine	Difference
Heart rate Beats per minute	87.4	91.1	+ 3.7	84.3	108.0	+23.7
Blood pressure Systolic mm Hg	132.2	162.9	+30.7	146.2	163.5	+17.3

15 minutes before and 15 minutes after yohimbine administration. The epinephrine dose was 0.20 γ/kg/min given intravenously over a period of three minutes.

As is seen from Table 2 epinephrine produced a significantly greater increase in heart rate after yohimbine than it did alone, an average

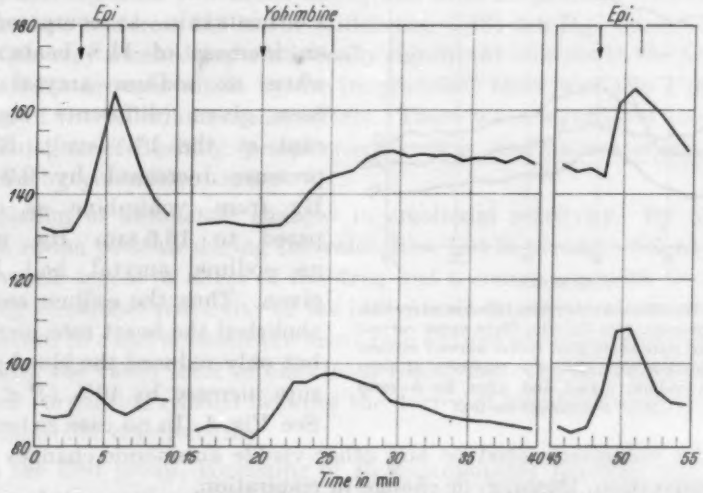

Fig. 3. The effect on systolic blood pressure mm Hg (upper curve) and heart rate beats/min. (lower curve) of epinephrine infusion (Epi), before and after yohimbine infusion. For dosage, see text

20 beats/minute more (range +6 to +38). This difference was significant at the 0.1% level. While in two cases the heart rate had decreased before, it now increased in all ten cases from epinephrine.

The blood pressure after yohimbine was elevated to a higher level than before. The increase obtained with epinephrine now was less marked, an average 13.4 mm Hg less (range −51 to +6). This difference was significant at the 5% level only. The actual blood pressure obtained with epinephrine was generally at least as high as before, except in two cases where the increase before yohimbine was unusually high (over 200 mm Hg). In these cases the blood pressure obtained after yohimbine was within a more normal range. See Fig. 3.

A further observation was that certain of the effects usually obtained with yohimbine, such as tremor, flushing and restlessness, became more marked when epinephrine was superimposed.

Effect of sedatives on the autonomic changes. Seven of the 10 subjects of the above group were given amobarbital sodium 6.25 mg/kg intravenously prior to the administration of yohimbine. The sodium amytal put all, except one, into a light sleep which lasted throughout the whole test period. Following the amytal, blood pressure was lowered and heart rate was somewhat accelerated. Yohimbine given at this point did not markedly change heart rate; there was a mean decrease of 1.6 beats/min. as compared to an increase of 11.8 beats/min. when no sodium amytal had been given (difference significant at the 1% level). Blood pressure increased by 9.9 mm Hg from yohimbine as compared to 16.6 mm Hg when no sodium amytal had been given. Thus the sodium amytal abolished the heart rate increase but only reduced the blood pressure increase by 40% ($P < .05$). See Fig. 4. In no case so treated did the yohimbine produce any other visible autonomic changes such as perspiration, flushing, or change in respiration.

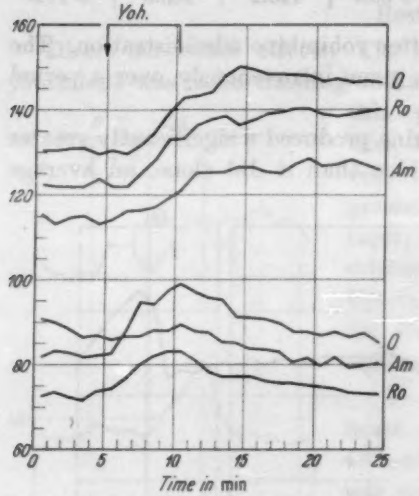

Fig. 4. The effect of yohimbine infusion on systolic blood pressure mm Hg (the three upper curves) and heart rate beats/min. (lower curves) without premedication (0), after i. v. injection of amobarbital sodium *(Am)* and after Ro 5—0690 *(Ro)*. For dosage see text

Ro 5—0690 (7-chloro-2-methylamine-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride[1]) 1.5 mg./kg. given by slow intravenous injection to the same seven individuals 15—20 minutes before the yohimbine test put only one of the subjects to sleep and made the others slightly drowsy. This level of depression was considerably less than seen with amobarbital; they could rationally respond to questions but with definite slurring of speech. Both heart rate and blood pressure were somewhat lowered by this drug. Yohimbine gave a heart rate rise of 6.7 beats/min. and a blood pressure rise of 15.8 mm Hg, which means a reduction by 43% ($P < .20$) and 5% (not statistically significant) respectively, compared with the response to yohimbine alone. The other visible autonomic changes were reduced but not to the same extent as with amobarbital.

[1] This preparation (Librium) was provided by Hoffmann La Roche Co.

Effect of medication with imipramine. Seven subjects (four schizophrenics, one alcoholic and two sociopaths) were studied to determine the effects of imipramine medication on the response to yohimbine. The imipramine was started after the first yohimbine test. The subjects were given a daily oral dosage of approximately 3 mg/kg body weight divided in three doses daily for three weeks, after which the second yohimbine test was carried out.

The average heart rate rise produced by yohimbine before imipramine was from 72 to 89 (difference +17) beats/min. The baseline heart rate was increased while on imipramine medication to an average of 96 beats/min, and there was a further rise after yohimbine injection to 125 beats/min. (difference +29).

The blood pressure increased from an average of 116 to 130 (difference +14) mm Hg from yohimbine alone, and after imipramine medication the increase was from 119 to 167 (difference +48) mm Hg. Concomitant with this very marked and statistically significant increase in the yohimbine effects brought about by the imipramine, there was also a potentiation of the other autonomic effects. There was a significant increase in the degree of flushing, perspiration, tremor, and nausea above that induced by yohimbine alone.

Relation of autonomic changes to emotional reactivity. By observation of the patients during the yohimbine test it became evident that the overall degree of effect of the drug had a connection with the preexisting emotional reactivity of the individual. A statistical correlation was shown to exist between the heart rate change obtained with yohimbine and the rated level of emotional reactivity. On the other hand, no such correlation existed between the degree of blood pressure change and emotional reactivity.

In the first group, consisting of 15 schizophrenic patients, the correlation between heart rate increase from yohimbine and emotional reactivity was .739 ($P<.01$). In the second group, consisting of nine normal volunteers, findings were very similar, and the correlation was .925 ($P<.01$). In the third group, consisting of 20 mental hospital patients with varying diagnoses, again a correlation could be shown to exist, $r_s=.605$ ($P<.01$). It could thus be safely stated that the heart rate increase obtained from yohimbine injection had a definite relationship to the basic emotional reactivity.

In none of these three populations did the degree of blood pressure increase have any significant correlation to emotional reactivity, $r_s=-.293$, .160, and .086 respectively. In the first group there was a correlation between the duration of the blood pressure increase and the emotional reactivity, $r_s=-.526$ ($P<.05$). No such correlation existed in the latter two populations.

In the first as well as in the second group the baseline heart rate (as measured in the experimental situation) before the test correlated equally well with emotional reactivity, $r_s = .732$ and 892 respectively ($P < .01$). In the third group the correlation was insignificant (.018) probably because these were patients that had become familiar with the various laboratory procedures. Only in the first sample did a significant correlation exist between baseline blood pressure and emotional reactivity, $r_s = .746$ ($P < .01$), while in the latter two the correlations were as low as .075 and $-.194$.

The effect on heart rate of preparatory procedures (insertion of an intravenous needle, injection of normal saline) correlated significantly with emotional reactivity in the first sample, $r_s = .610$ ($P < .05$), while the correlations in the second ($r_s = .579$) and in the third (.377) were not significant. There was a significant correlation between the rise in heart rate from the preparatory procedures and that from yohimbine injection, $r_s = .753$ ($P < .01$) in the first group, and in the second $r_s = .667$ ($P < .05$). In the third the correlation (.338) was not significant. Only in this last group was there a very significant correlation between emotional reactivity and the blood pressure effect of the preparatory procedures, $r_s = .697$ ($P < .001$). In the first two groups the correlations were not significant.

The relationship found between emotional reactivity and the effect of the drug on heart rate was evidently fairly independent of diagnostic categories. It existed in the first schizophrenic group as well as in the normal volunteers. It also existed in the third group, consisting of both psychotic and non-psychotic mental hospital patients. When this latter group is broken up into one part consisting of 12 schizophrenic patients and one part consisting of eight non-schizophrenic patients (psychopathic and alcoholic cases and one case of syphilitic brain damage), the correlation within each of the parts is somewhat higher than for the total group (.729 in the schizophrenic group and .792 in the non-schizophrenic group). When the heart rate increase from yohimbine in the 12 schizophrenics is compared to the increase in the eight non-schizophrenics, there is no significant difference. The range of heart rate change (mean over a 5 minute period) in the schizophrenic group was -1.0 to $+22.4$ (mean $+10.2$), and in the non-schizophrenic group $-.2$ to $+27.2$ (mean $+10.0$) beats/min. This lack of difference is apparently due to the fact that the schizophrenic patients showed all degrees of emotional reactivity, from strongly over-reactive to very unreactive states (score .7—6.1, mean 2.40), while the non-schizophrenic cases were scattered in a similar way, only within a somewhat narrower range (score 1.3—4.8, mean 3.25). The latter material of 20 cases was checked for possible correlations between drug effect on the one hand

and age, time of stay in the hospital, and body weight on the other hand. None of these correlations was significant even on the 10% level.

To date only one depressive has had the yohimbine test, a 48 year old man who has had two manic episodes on previous occasions and this time was admitted with endogenous depression. He was almost mute, showed signs of great fear and anxiety, and had classical delusions of a melancholic type. This case showed the most marked heart rate and blood pressure changes that we have seen. The maximum heart rate was 136 beats/min. and maximum blood pressure 208 mm Hg. It took more than one hour before these changes had subsided. Also salivation, flushing, sweating, and lachrymation were of severe degree. Erection was also observed.

Psychic effects. Concomitant with the autonomic response to yohimbine, psychic changes were also observed, simulating an anxiety state. The subjects displayed a tense and anxious facial expression. They became restless, irritable, tremulous, and feelings of impatience and unrest were often experienced. In the few cases where this state was very marked it usually coincided with feelings of nausea. The most affected subjects showed a marked reluctance toward repeating the yohimbine test. Apparently the anxiety and fear induced by the drug remained clearly in the subjects' mind, which is in keeping with the observation that the drug did not cause confusion.

Premedication with amobarbital sodium (see above) completely abolished all subjective sensations induced by yohimbine, and only slight restlessness was observed whilst the subjects were asleep. Ro 5—0690 also reduced feelings of anxiety and tension but not to the same degree as the amytal. Medication with imipramine greatly increased the severity of the psychic changes induced by yohimbine. The tremor and restlessness became so marked in several cases that it amounted to an acute panic. This potentiation from imipramine was such that even in previously unreactive subjects the response induced by yohimbine produced definite tremor, restlessness, tension and anxiety.

In a group of five schizophrenic subjects yohimbine was given intramuscularly three times per week in doses dependent on the degree of response produced in the individual patient (range 20—40 mg. per dose). Usually the dosage was eventually increased, as a degree of tolerance appeared to occur, but maximum was kept at 40 mg. Of these five subjects, two showed a minimal over-all response to the injections. One was a schizophrenic in a state of remission with some remaining apathy and lack of initiative. The other was an extremely withdrawn, anergic, unresponsive little man who did not speak spontaneously at all and would reply to questions in monosyllables. The only significant effect produced with yohimbine was restlessness, tremor and slight

anxiety-type response in the latter case. However, they both became more active, alert, outgoing and generally more responsive. The first case was released from the hospital after termination of medication, but this may have had no relation to the medication. The other patient did not maintain this change after cessation of yohimbine.

The other cases also become more active and mobile, but their behavior was more disturbed. One admitted to auditory hallucinations and sat about muttering. All three became grossly disturbed for a period of about one hour after each injection of yohimbine. They actively hallucinated, laughed and addressed their hallucinations loudly, and made fists and threatened imaginary people and objects. This acute response completely subsided in the latter part of the day and they were then more alert, active and responsive than usual and a little euphoric. These effects were no longer present the next day.

The one depressive case studied showed initially a classic picture of endogenous depressive psychosis. He was inactive, hypochondrial, self-deprecatory and nihilistic. His speech was very retarded, and at times he was almost mute. After about one week on treatment his depression became definitely less severe, sleep improved, conversation was freer, and he was less nihilistic. But towards the end of the second week his condition was again approximately the same as at the commencement of treatment. He then progressively became worse, which necessitated discontinuance of yohimbine. At the end of the third week his condition was one of severe agitated depression with suicidal thoughts. E. S. T. was instituted, and significant improvement resulted but inadequate for release to be even considered.

Discussion

It should be pointed out that the methodology employed in this study is in several respects different from that used in most of the established autonomic drug tests. In the procedures suggested by FUNKENSTEIN et al. (1950) and by HOFFER and CALLBECK (1959b), epinephrine is given in a rapid intravenous injection, and methacholine and atropine have been given by the intramuscular route, all drugs in fixed standard doses. These procedures do not control for variable absorption from the i. m. route, dosage is not corrected for body weight, and, finally, speed and rate of intravenous injection are not defined. Age is a further factor which has been shown to be of importance (NELSON and GELLHORN) but is usually not controlled. On the basis of the findings with two different drugs, FUNKENSTEIN classifies his cases into categories which seem rather arbitrarily constructed without regard for the fact that the epinephrine *per se* does not seem to contribute to the resulting correlations (FUNKENSTEIN et al. 1952). For correlation with

these categories such complex factors as clinical diagnosis and the outcome of E.C.T. and other treatments have been chosen. More recent studies have questioned the reliability of these methods (MAAS; JANG) and furthermore have failed to substantiate many of the original findings (SLOANE et al.; LUNDE et al.; HOFFER and CALLBECK 1959a; SATTERFIELD; OZTURK et al.; BRAUN and RETTEK; BRILL et al.).

The experimental procedure adopted in this study is so designed as to control for the variables of body weight, absorption, and speed of administration. Possible correlations with age are checked. Also, we attempt correlation only between the actual quantitative responses obtained and the rating of a single fairly well-defined clinical variable, viz. the overall emotional reactivity. In individual cases observer error may introduce an inaccuracy in rating. Over a series of 60 cases, however, these random variations should cancel and allow an accurate assessment. There are no signs of correlation between test results and diagnosis, and no attempt is made at correlating test results with prognosis which is a still more complex factor. A direct comparison between our results and those of the FUNKENSTEIN group is not possible.

The effects produced by yohimbine are both adrenergic and cholinergic in nature. Flushing, sweating, salivation, lachrymation, urgency and frequency of micturition and defecation can likewise be produced by intravenous metacholine and may be considered to be predominantly cholinergic effects; whereas mydriasis, blood pressure increase, and perhaps tremor and tachycardia may be considered to be adrenergic type responses.

The usual psychic effect produced by yohimbine in our subjects was an anxiety-type state. Similar effects have been reported from injected epinephrine, and the utilization of such drug-induced psychic responses has been investigated by other workers (LINDEMANN and FINESINGER; FUNKENSTEIN et al. 1950). The anxiety response from yohimbine is, however, much greater than with epinephrine. Similar type responses may occur with other sympathomimetic amines (IVY and KRASNO) and with the indole alkaloid ibogaine (SCHNEIDER and SIGG). These effects of yohimbine are, therefore, certainly of central origin.

The adrenolytic properties ascribed to yohimbine in the literature (RAYMOND-HAMET; BARRY; YONKMAN et al.; BOVET and BOVET-NITTI; NICKERSON; GOODMAN and GILMAN) were not observed in our study. This is most likely due to the much larger dosages (minimum 2—7, usually 15—30 mg/kg) employed in the animal studies compared to our dosage of 0.5 mg/kg. JANG (1941) using very low concentration of yohimbine showed that it sensitized the perfused rabbits' ear to epinephrine. A similar phenomenon was also observed in our study

in that both the heart rate effects, tremor and psychic actions of epinephrine were markedly potentiated by a previous yohimbine dose.

The central nervous system depressants and stimulants studied inhibited and potentiated, respectively, both the autonomic and the psychic effects of yohimbine. This supports the view that the yohimbine effects are to a great extent centrally mediated (cf. BOVET and BOVET-NITTI). This applies to all the effects of yohimbine except the rise in blood pressure, which was only partially reduced by premedication with amytal.

The degree of autonomic and psychic responsiveness to yohimbine was shown in three separate populations to be correlated with the basic emotional reactivity, irrespective of diagnostic category, of age and body weight. Of the autonomic measures, this responsiveness is reflected most accurately in the heart rate but not to any significant degree in the blood pressure. This test procedure can, therefore, give an index of responsiveness of the centers of emotional and autonomic reactivity in the thalamo-hypothalamic area.

Yohimbine was also found to activate the more or less latent psychotic process in some of our schizophrenic subjects. There was an increase in general reactivity, active hallucinations, expression of delusions and demonstrations of disturbance in behavior. Two other indole alkaloids, ibogaine and harmine, have been reported to have psychotomimetic effects with the production of excitement, inebriation states, mental confusion and hallucinations. All three indole alkaloids show distinct central nervous system stimulant properties. As regards ibogaine, the findings indicate involvement of cholinergic mechanisms in the production of central stimulation (SCHNEIDER and SIGG). However, it is difficult to ascribe all the effects of yohimbine solely to the cholinergic effects, as adrenergic stimulation is obviously also involved. This may account for the differences seen with these two compounds although there is a basic similarity in their effect.

Our findings indicate that yohimbine has marked autonomic and psychic effects which can be utilized for further studies. The almost specific anxiety-like response induced by yohimbine and its relationship with the basic level of emotional reactivity of the subjects is also of interest for further studies. Further, in psychotic subjects, excluding very chronic deteriorated subjects, yohimbine seems to produce activation of the psychotic picture. It would be of interest to study its effect on latent schizophrenic reactions. It is felt that studies with this compound may be especially useful in studying the problem of reduced autonomic and emotional responsiveness in deterioration of diverse origins. It may be helpful in elucidating relationships between emotional phenomena and autonomic responses in normal and mentally ill subjects.

Summary

Yohimbine in a dose of 0.5 mg/kg has been given to 51 male mental hospital subjects and nine normal volunteers.

It has produced both cholinergic and adrenergic-type autonomic effects and psychic effects simulating an anxiety state. The degree of both these responses to yohimbine correlates highly with the basic level of emotional reactivity.

Central nervous system depressants, amobarbital and Ro 5—0690, reduced the degree of response to yohimbine, whilst the CNS stimulants imipramine and epinephrine potentiated the yohimbine effect. Yohimbine in the dosage here employed did not have any blocking effect against injected epinephrine.

Activation of the psychotic picture was produced by yohimbine in some schizophrenic cases.

Yohimbine is a promising compound for use as an autonomic test drug.

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Clinical Reports · Klinische Mitteilungen · Communications cliniques

Chlorpromazine in Chronic Schizophrenic Women:

I. Experimental Design and Effects at Maximum Point of Treatment*

By

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With 12 Figures in the Text

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The present study was designed to compare the effects of chlorpromazine, phenobarbital, and placebo in a randomly selected sample of chronic schizophrenic women in a state hospital setting. The purpose of this study was to determine the possible therapeutic efficacy of chlorpromazine and to describe the effects of this agent in several areas of psychological functioning.

The most comprehensive review of controlled studies with chlorpromazine which has come to our attention is that of HEILIZER (1960). His annotated bibliography includes reference to over 60 titles in which chlorpromazine effects are compared with placebo controls. The inherent difficulties in this area of research are sharply highlighted by his critical analysis of these articles. The application (and sometimes misapplication) of a great number of variations in methodology, design, subjects, and analysis of results may be a basis for the seemingly contradictory conclusions often reported.

One of the most extensive controlled investigations of chlorpromazine was the Veterans Administration study recently summarized by CASEY et al. (1960). Thirty-seven hospitals contributed nearly 700 male subjects to the experiment in which the therapeutic superiority of chlorpromazine over phenobarbital and placebo was demonstrated. The Multidimensional Scale for Rating Psychiatric Patients (LORR et al. 1953) was the principal measure of change. This report is particularly convincing in view of the extremely large sample, objectively evaluated

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with a uniform experimental design and double-blind controls. In conjunction with findings from other controlled studies it leaves little doubt of the general clinical efficacy of chlorpromazine in schizophrenia.

The present study concerns women and is designed to describe chlorpromazine effects in some detail through a more intensive investigation with fewer subjects randomly selected from a larger population. It has a number of aspects which will be reported in stages. This, the initial paper, emphasizes research design, methods of evaluation, and the effects of drugs at the point of maximum treatment. It includes data simultaneously obtained from the psychiatric examination, scaled observations of ward behavior, psychological tests, and scaled observations of the psychologists who tested the patients.

Method

Subjects

Selection of subjects. The subjects for this study were female patients randomly selected (table of random numbers) from the population of Central State Griffin Memorial Hospital, Norman, Oklahoma. Each patient met the following criteria:

a) Diagnosis: Schizophrenia.

b) Minimum hospitalization: 5 years.

c) Age range: 25—50 years.

d) No recorded evidence of mental deficiency, epilepsy, CNS syphilis, or other types of organic brain disease.

e) No recorded history of brain surgery of any type.

f) No recorded or current evidence of metabolic disease, liver disease, or heart disease.

These criteria assured the chronicity of the illness and eliminated the confounding effects of known brain damage. In addition, the elimination of subjects with medical complications provided a group that was less likely to have a high attrition rate in a relatively long term study. Approximately 600 female patients in the hospital met the first three criteria but less than 200 met all criteria. From this latter group 64 subjects were selected at random (table of random numbers).

These subjects were assembled on a special research ward and observed for 13 months prior to initiating the formal study. During this period four subjects were removed from the group, leaving a total number of 60 patients. One was eliminated because of rheumatic heart disease, another because of chronic renal disease, and 2 were selected at random to participate in a pilot study.

Description of sample. During the 13 months of preliminary observation all somatic therapies were discontinued. Forty-five patients had previously received psychoactive drugs and 29 of these were receiving drugs at the time of their transfer to the research ward. None experi-

enced noticeable withdrawal symptoms but many appeared to deteriorate psychiatrically over the year. This preliminary period allowed the effects of previous treatments to dissipate and enabled the patients to become accustomed to their new environment and the ward personnel prior to initiation of the drug trial. No spontaneous remissions occurred.

The diagnosis of chronic schizophrenia for each experimental subject was confirmed by the team psychiatrist, using the criteria of the diagnostic manual of the American Psychiatric Association (1952). A breakdown of descriptive data is given in Table 1.

The symptomatology of the group just prior to initiation of drug therapy will be relevant for the purpose of understanding drug effects. Considerable diversity was found in all categories.

a) Appearance: Most patients neglected their grooming and appeared to lack interest in appearance and personal hygiene, while an occasional patient decorated herself or used clothing and cosmetics in a bizarre fashion.

b) Communication: Many patients were unable to engage in a meaningful conversation. Only 20 patients were able to give a reliable account of their past lives; the remainder of the narratives were lacking in details, accuracy, and emotional depth. Thirty-three patients, although willing to talk, could not express themselves coherently. Their expressed thoughts sometimes seemed dissociated and to lack direction or purpose. They frequently employed symbolic forms of speech and neologisms. Seven patients refused to communicate verbally, although one of these was willing to answer questions in writing. Seldom were patients able to give a reasonable explanation of why they were hospitalized. Common themes in their statements of life history were poor schooling, unsatisfactory occupational adjustment, inability to establish close emotional ties with others, and poor sexual adjustment, ranging from promiscuity to complete withdrawal from heterosexual activities.

c) Affect: Thirty-three patients showed marked abnormalities of affect such as apathy, lack of emotional responsiveness, bewilderment, or elation.

d) Delusions and Hallucinations: Markedly delusional ideas were elicited in 22 subjects. Ideas of persecution, immeasurable wealth, power, status, being victims of sexual assaults and the objects of horrible punishments were among the most common. Twenty-one patients appeared to suffer from hallucinations which were predominantly auditory although some were visual and somatic.

e) Activity: Some patients seemed restless or talked incessantly while others seemed quite withdrawn and spent much of their time either in bed, or standing or sitting motionlessly.

f) Interest and Initiative: Most patients expressed very little interest in their future. Many of them even professed satisfaction with their institutional life.

Table 1. *Characteristics of the sample*

	Total Mean (range)		Chlorpromazine Mean (range)		Phenobarbital Mean (range)		Placebo Mean (range)	
Age (years) . . .	43.0 (26—52)		41.2 (26—51)		44.3 (29—52)		43.6 (33—50)	
Years in hospital this stay . . .	13.0 (3—24)*		12.7 (3—24)*		12.5 (5—21)		13.8 (7—24)	
Years since first admission. . .	14.6 (3—27)*		13.8 (3—26)*		14.0 (7—27)		16.1 (8—26)	
Education: Years Schooling	9.9 (1—16)		10.0 (1—14)		10.3 (6—13)		9.2 (2—16)	
	Frequency		Frequency		Frequency		Frequency	
Schizophrenic Reaction Type:								
Simple	12		7		2		3	
Hebephrenic .	17		5		7		5	
Catatonic. . .	9		3		2		4	
Paranoid . . .	19		4		8		7	
Residence:								
City	18		8		6		4	
Town	12		5		3		4	
Farm	15		4		6		5	
Unknown . .	12		2		4		6	
Marital Status:								
Previously married . .	42		14		13		15	
No previous marriage . .	15		5		6		4	
Number of children:								
None.	24		8		10		6	
1—3	25		8		7		10	
4 and over . .	8		3		2		3	
	Yes	No	Yes	No	Yes	No	Yes	No
Previous Treatment								
E.C.T.	50	7	17	2	15	4	18	1
Metrazol . . .	12	45	3	16	3	16	6	13
Insulin	18	39	7	12	7	12	4	15
Chemotherapy	45	12	17	2	14	5	14	5
Relatives in this hospital . . .	28	29	9	10	10	9	9	10

* At the completion of this study it was determined that one patient had been hospitalized here only 3 years and one 4 years. Both had a longer record of illness.

Just prior to initiation of experimental treatments the patients were extremely regressed and showed, in one manner or another, the profound disruption of psychological processes characteristic of chronic schizophrenic women after long hospitalization.

Experimental design

At the end of the 13-month observation period, the 60 subjects were rated on the Oklahoma Behavior Scale and, on the basis of these scores, were individually matched into triplets. Random assignment of triplet members to treatment groups resulted in 3 matched groups of 20. Each group was later reduced to 19 subjects by removal of a triplet when one of its members developed agranulocytosis in the twelfth week of chlorpromazine treatment.

The double-blind procedure was followed throughout. Neither the patients nor the personnel involved in the care or evaluation of the subjects were informed of any individual's medication until the end of the study. Medications were dispensed in individually labeled bottles so that identification by code was not possible.

Medication was administered orally according to the schedule in Table 2. All groups were administered 1 placebo capsule twice daily

Table 2. *Schedule of dose levels and measurements*

	Weeks of the study					
	4	8	12	16	20	24
Daily dose levels						
CPZ (milligrams) $n = 19$						
Maximum	*	*	600	800	800	800
Mean			600	779	721	663
Minimum			600	400	300	200
Barb. (milligrams) $n = 19$						
Maximum	*	*	360	480	480	480
Mean			347	423	394	388
Minimum			240	120	120	120
Placebo (capsules) $n = 19$						
Maximum	2	2	6	8	8	8
Mean	2	2	6	8	8	8
Minimum	2	2	6	8	8	8
Schedule of measurements						
Psychiatric Examination	×					×
Behavior Scale	×	×	×	×	×	×
Purdue Peg Board I and Digit Symbols	×	×	×	×	×	×
Psychologists' Scale	×	×	×	×	×	×
Names Known, Time Estimation, D.C.T., Purdue Peg Board II	×	×				×

* During the first 8 weeks all patients in all groups were given 2 capsules of placebo daily, following which the Chlorpromazine (CPZ) and Phenobarbital (Barb.) patients were switched to their assigned drugs in identical capsules. The unit capsule contained either 100 mg CPZ, 60 mg Barb., or similar appearing amounts of placebo (lactose). The number of capsules required for the drug groups was the same as in the placebo group for the patients receiving maximum dose.

during the first 8 weeks. Thereafter, each group received its assigned medication in identically appearing capsules as follows: First week, 1 capsule twice daily; 2nd week, 2 capsules twice daily; 3rd and 4th weeks, 2 capsules three times daily; thereafter for 12 weeks the medication was given in 2 capsules, 4 times daily unless individual adjustments were made. The maximum daily doses were: chlorpromazine, 800 mg; phenobarbital, 480 mg; and placebo, 8 capsules. Adjustment of dosage was necessary in approximately 50% of the phenobarbital and chlorpromazine groups when toxicity and over-dosage became apparent (primarily in the later weeks of the study). The maximum, minimum, and average daily dose is shown in Table 2.

To be certain that medications were being taken, careful attention was given to each individual during the administration of capsules. When occasional patients were unable to swallow the capsules, the contents were administered suspended in a liquid quinine solution, thereby disguising the taste. Urine tests for chlorpromazine (FORREST and FORREST 1957, FORREST et al. 1958) during the 23rd week indicated that the subjects were properly receiving their assigned medications.

Treatment effects were evaluated independently by the psychiatrist, the ward attendants, and the psychologists according to the schedule shown in Table 2. All evaluation procedures were employed during the placebo baseline period (8th week) and again during the maximum treatment period (24th week). Some measures were repeated at 4-week intervals throughout the study.

In order to allow one psychiatrist to examine all patients and to permit the psychologists and psychiatric aides to test and rate only a small number of patients weekly, a staggered schedule was adopted. Five patients from each treatment group were randomly assigned to each of four examination groups. Each successive group started and ended the study one week later than the preceding group, i.e., the 2nd examination group began and finished the study 1 week later than the 1st group, and the 3rd group one week later than the 2nd group, etc. All treatment groups were equally represented in each of the examination groups so that any systematic effects were equally distributed.

During the 13-month preliminary period and throughout the study an attempt was made to continue the same milieu and administrative attitude in the ward management. Auxiliary individualized treatment such as E.C.T., psychotherapy, and other tranquilizers were entirely avoided. Recreational activities, movies, religious services, occupational and recreational therapies were available routinely on a regular schedule and all patients were allowed to attend these activities according to their own interests. Infrequently, the attendant or nurse in charge would deny the request of a patient to attend an activity off the ward

if the patient appeared to be unable to conform to the standards of conduct demanded by the specific activity. On the ward, judicious use of fast acting barbiturates, restraint and seclusion were the sole methods of drastic control of unmanageable behavior.

Evaluation techniques

Psychiatric examination. Psychiatric interviews of approximately one hour duration were conducted with all patients in the 4th (placebo) week of the study and repeated in the 24th (peak dose) week. The individual interviews were designed to obtain information in various categories of psychopathology. This information was recorded immediately after each interview, and together with the information obtained from routine ward rounds, formed the basis for psychiatric judgements concerning clinical improvement.

A patient was judged clinically improved if one or more of the following criteria were met:

a) Reduction of behavior causing pain to others, such as a diminution of openly hostile verbal or physical behavior, noisiness, provocative and destructive actions.

b) Diminution of painful subjective experiences, such as decreased anxiety, disappearance of despondent feelings, disappearance of fear, which in general indicated the patient felt more comfortable.

c) An increase in ability to communicate thoughts with clarity, and to convey needs to others.

d) Diminution or disappearance of delusional ideas and hallucinations.

e) Increased interest in future and attempts to make plans to live again in society.

f) Change in affect so that it was more appropriate to the situation.

g) Increased interest in personal appearance and hygiene, as well as diminution in exaggerated and bizarre types of dress.

In addition to providing narrative descriptions of change and judgments concerning clinically significant improvement, the psychiatrist at the conclusion of the study ranked all patients according to his impressions of their degree of change.

Oklahoma Behavior Rating Scale. This scale was developed specifically for the use of psychiatric aides on this research ward. The format and items are primarily a composite of several existing scales. The language level and mechanics of scoring were developed in close collaboration with the aides. It evolved as a forced choice scale with concrete behavioral descriptions requiring a minimum of interpretation by the rater. Although experience with it has made certain modifications seem desirable, the usefulness of this scale for detecting changes in behavior is

borne out empirically by the results of its present application and by the results of earlier validity and reliability studies.

An initial inter-rater reliability study was conducted during a preliminary experiment with 24 patients. Correlation coefficients between pairs of raters on the gross behavioral pathology score (TB) were .94, .80, and .99. It was recognized that the reliability of ratings might suffer through continued use of the scale and a second reliability check was undertaken during the 32nd week of the present study. Fifty-nine patients were rated by the 3 regular raters and 2 alternate raters, in various combinations of pairings. It may be observed in Table 3 that although the reliability was not quite as high in all cases as the earlier study, it continued to hold to a satisfactory degree.

Table 3. *Reliability between pairs of raters for 59 subjects on 7 summary scores of the Oklahoma Behavior Scale evaluated in the 32nd week of the study*

Summary score	r
TB : Typical Behavior	.82
TB+: Typical overactivity . . .	.72
TB−: Typical underactivity . .	.79
EB : Extreme Behavior	.80
EB+: Extremes of overactivity	.85
EB−: Extremes of underactivity	.87
BV : Variability of Behavior . .	.65

Prior to the present study the validity of the scale was evaluated in three ways. First, a male maximum security ward ($n=27$) on which the difficult behavior problems of the hospital were assembled was compared with a male open ward ($n=42$) where patients were assigned because they did not present behavior problems. The ranges of behavior scale scores were essentially mutually exclusive and significantly different on X^2 analysis ($p<.001$). Second, in a preliminary drug evaluation study, the patients ($n=23$) were divided into groups corresponding to the psychiatrist's impression of favorable change, no change, and unfavorable change. The behavior scale change scores for these three groups were also found to be significantly different by analysis of variance ($p<.001$). Third, the changes in behavior scale scores for 23 patients during the same

Table 4. *Agreement (correlation) between changes seen in Behavior Scale scores and changes seen in other test scores during drug treatment ($n=23$)*

	Behavior scale r
Ranked Improvement (by Psychiatrist)	.68**
Purdue Peg Board	.72**
Digit Symbols (WAIS)	.78**
Comprehension (WAIS)	.71**
Similarities (WAIS)	.46*
Raven Progressive Matrices	.63**
Drawing Completion Test (Wartegg-Kinget)	.57**
Time (Progressive Matrices)	.64**
Time (Drawing Completion Test) . . .	.57**

Probability levels: * less than 0.05, ** less than 0.01.

study were found to be significantly correlated with changes in scores from several psychological tests on the same patients (see Table 4). The behavior scale changes correlated significantly with those from each of 9 other measures. On the basis of these findings, the reliability and validity of the behavior scale was judged to be adequate for its present application.

The scale, as used in this study, consisted of 9 items, each with a thirteen-point scale ranging from +6 through 0 to −6. "Plus" values generally represent outgoing behavior or overactivity, while "minus" values represent seclusiveness or underactivity. "Zero" represents the kind of behavior which might ideally be expected of an ordinary non-schizophrenic person behaving in a socially decorous manner. The 9 items on the behavior scale are: Communicativeness, Activity, Aggressiveness, Sociability, Grooming, Mood, Toilet Behavior, Attitude Toward Medication, and Eating Behavior.

The first item will serve to illustrate the format of the scale[1].

Communicativeness.

+6) Very loud: May shout or scream or behave boisterously.
+4) Rapid speech: Talks most of the time, may not care what he says, talks whether someone is listening or not.
+2) Talkative: Does most of the talking in a conversation; it may be difficult to get ideas across to the patient due to his continuous flow of words. Patient does not usually talk to himself, however.
0) In good contact: Can and will talk to others with meaning, will also listen and understand others. Some irrational ideas are permissible, the main thing is the capacity to interact, to give and take in a conversation.
−2) Usually quiet: Does not say much, seldom starts a conversation, will answer questions but does not volunteer information.
−4) Uncommunicative: Close mouthed, reserved, speaks only when absolutely necessary or when pushed to speak.
−6) Mute: Ordinarily says nothing even in reply to direct questions.

Seven separate summary scores were derived from this scale, each providing information different from the other.

TB: The "Typical Behavior" score is the summation of item scores disregarding the direction from zero. It is the extent of deviation of behavior reflected on the scale and can be referred to as "gross behavioral pathology score." It is concerned with the typical behavior of the patient during the 2 week period immediately preceding the rating.

TB+: The "Typical Behavior plus" score is the summation of item scores which fall on the plus side of zero. Overactivity and outgoingness were thus analyzed separately from their opposite.

TB−: The "Typical Behavior minus" score is the summation of item scores which fall on the minus side of the zero. Thus, underactivity and seclusiveness were also analyzed separately.

[1] A copy of the full scale may be obtained from the authors.

Extremes of behavior were also summarized. This scoring was initiated at the request of the raters who felt during previous studies that it was often difficult to fix a patient on the scale who was quite variable in behavior. It was decided to *circle* on the scoring sheet the description which was most typical of the patient (see "T" scores above), but also to *check* all descriptions of behavior which were applicable to the patient at any time during the rating period. The most extreme behavior recorded on each item was used as the score.

EB: The "Extreme Behavior" score was derived by summing the EB + and EB — scores.

EB +: The "Extreme Behavior plus" score was derived by summing the score values of the most extreme score checked for each item which bore a plus sign.

EB —: The "Extreme Behavior minus" score was derived by summing the score values of the most extreme score checked for each item which bore a minus sign.

The "E" score analysis provides a method of determining the effects of treatment on the most extreme behavior manifestations which were seen during the particular rating period. This score, in addition to making the rating task more sensible to the raters, is possibly quite important in the evaluation of psychiatric patients. Many of them may behave typically in a "normal" way, but nevertheless display occasional deviations into disturbed behavior. It would, therefore, be unrealistic to characterize them solely according to one or the other.

BV: The "Behavior Variability" score was derived by summing the *range* of extreme scores within each item. It provides an index of variability of behavior seen during each rating period.

Ratings on this scale were carried out by three psychiatric aides so that all patients were rated at 4 week intervals. The staggered schedule of the design allowed each rater to rate no more than 5 subjects each week with each rating based on observations made over the previous 2 weeks.

Psychological tests. The Purdue Peg Board, Digit Symbols, and Psychologists' Ratings were administered at the end of each 4 week period throughout the study.

a) The Purdue Peg Board (TIFFIN and ASHER 1948) is a simple motor task requiring the subject to pick up steel pegs, washers and sleeves, one at a time, and insert them in holes on the board or assemble them as rapidly as possible for a set number of seconds. Both hands are used singly and in combination in various sections of the test which requires 150 seconds of total testing time. The score is the number of pegs inserted or pieces assembled.

b) The Digit Symbols test (WECHSLER 1955) is a standard sub-test of the Wechsler Adult Intelligence Scale (WAIS). The test is a clerical coding task requiring the patient to scan a code and copy the proper symbols under numbers which appear in random order on an answer sheet. The standard time of 90 seconds was used. The score is the number of correct symbols copied. In order to minimize learning effects on repeated exposure to the test, nine alternate forms were used in which the symbols were randomly reassigned for each successive date of measurement.

c) The Psychologists' Rating Scale was used by the psychologists following the routine examination of each patient every 4 weeks. It was designed to reflect the style of participation in the examination, interpersonal behavior, and general appearance of the patient at the time of the examination.

The items included in the scale were taken from notes and narrative descriptions which had beem made in earlier studies. Of the 8 items originally designed 2 were discarded because of lack of reliability. The 6 items which were retained were titled: Ideational Fluency, Expressiveness and Gestures, Affect, Motor Activity, Ease of Testing, and Cigarette Smoking Behavior.

The format of the scale was the same as used for the Behavior Scale. The Ideational Fluency item will serve as an illustration:

+6) Patient chatters incessantly in disorganized way or shouts unintelligibly.
+4) Patient insistently presents psychotic ideas to examiner, is so preoccupied with own productions that examiner has difficulty breaking into stream of ideas.
+2) Patient is overtalkative but interacts with examiner to satisfactory degree.
0) Patient exchanges ideas spontaneously with examiner without loss of ease.
−2) Answers questions without spontaneously elaborating. Does not carry her end of the conversation.
−4) Verbally inhibited, replies with minimum answer to direct questions only. Requires urging to reply, may speak in monotone or muffled or faint speech.
−6) Muteness, or absence of meaningful speech (may mumble to self).

As in the Behavior Scale the "P" (Psychologists' Scale) scores represent the summation of item score deviations from zero. Three summary scores were calculated: They are "P", the summation of deviations disregarding sign; "P+", the summation of overactive deviations; and "P−", the summation of underactive deviations.

The reliability of these scores was sampled during the 32nd week of the project. While the regular examiner was seeing his patients one of the other psychologists sat at a desk in the same office, "eavesdropping" on the examination, following which each psychologist independently rated the patient on the scale. Independence of ratings

was ensured by eliminating discussions between raters until a total of *21* patients had been evaluated by two raters each. Correlation coefficients for $n=21$ were .91, .94, .97 for "P", "P+", and "P—" respectively.

At the 4th, 8th, and 24th weeks the psychologists employed several additional measures:

d) In the Time Estimation series each patient was instructed to take note of the passage of 5 seconds which the psychologist demonstrated with a stop watch. The patient was then asked to estimate the passage of 10 seconds from the signal to start. The procedure was then repeated for 20 seconds. Estimates of 10 and 20 seconds were taken three times at spaced intervals during the same examination. The score was the total number of seconds error accumulated in the six estimates (each estimate being limited to a 60 second maximum).

e) In the Names Known procedure the subject was asked to recall the names of as many patients on her ward as she could while the psychologist wrote them on the examination record. Credits were greater for complete names. This procedure was employed for the purpose of evaluating the level of social awareness among the patients. Overt social interaction among mental patients is notably less than among normals, as can be observed in ward behavior. It was theorized that increased knowledge of the names of other patients would reflect increased social awareness. Expansion of this test into a standard sociometric device was not possible since most of the patients expressed complete neutrality and refused to make favorable or unfavorable evaluations of one another.

f) The Drawing Completion Test (KINGET 1952) was administered to groups of 5—10 patients at one time during placebo baseline and peak dose periods. The test blank consists of eight squares enclosed in a heavy black border in each of which the patient was requested to make a drawing. A few marks are already present in each square and the expectation is that the subject will complete a drawing of some sort in each square utilizing the existing stimuli in some way. Each square was scored separately according to three criteria. A five point scale was used as follows:

Use of Stimulus
- 0 — No drawing
- 1 — Failure to use existing stimulus
- 2 — Pedantic repetition of stimulus
- 3 — Acceptable use of stimulus in a simple drawing
- 4 — Use of stimulus in an elaborate drawing

Content
- 0 — No drawing
- 1 — Scribbles
- 2 — Symbols and designs
- 3 — Objects
- 4 — Animate figures

Depth of drawing
0 — No drawing
1 — Simple lines
2 — Two dimensions, surface appearance
3 — Three dimensions, solid objects represented
4 — Distance, vista, perspective in space

A booklet was devised in order to help resolve scoring problems. Correlation between pairs of scores exceeded .93 in a series of 27 scoring problems. Although it was not structured as a speed test the amount of time spontaneously consumed by each patient was noted as she turned in her drawings and left the room. The maximum time allowed was 15 minutes.

g) The Purdue Peg Board (Pegs II) was administered a second time near the end of the examination at placebo baseline and peak dose.

h) Attendance at Off-Ward Activities reflects primarily the initiative and spontaneous interests of the patients. Throughout the study the subjects were allowed to attend off-ward recreational activities such as movies, religious services in the chapel, beauty parlor, library, canteen, Occupational Therapy, and Recreational Therapy. In addition, they assisted in off-ward housekeeping activities such as unattended trips to the laundry and trash disposal. All patients were notified of the activities as they occurred and those who wished to participate were permitted to do so, except rarely when judged unable to meet the standards of conduct for the particular activity. A daily check list record was kept for each individual.

The score for each individual consisted of the total number of times off-ward activities were attended during a given period of time. In the present study the frequency of attendance was recorded during the initial 8 weeks on placebo, and again during the final 8 weeks of the drug administration period.

i) In addition to the measures reported in this paper, skin resistance, oxyhemoglobin reduction time, blood pressure, pulse rate, temperature, body weight and other measures were taken at various stages of the study which will be reported subsequently.

Results

Clinical findings

Following the final examination of all patients at the 24th week the psychiatrist felt that only 8 patients (6 chlorpromazine and 2 phenobarbital) had clearly exhibited clinically significant improvement. Statistical analysis (FISHER'S exact method) of the frequency distribution revealed a significant difference between chlorpromazine and the other 2 groups ($p < .05$). The nature and degree of these changes are described below in brief case reports:

Chlorpromazine treated patients. A.F. (Schizophrenic reaction, Hebephrenic type; maximum tolerated dose = 600 mg; length of hospitalization 10 years). This patient was a 37-year-old female who wandered aimlessly on the ward. She giggled continuously without apparent reason, her speech was incoherent, and she expressed herself only in disconnected sentences.

After medication her giggling ceased and she was able to give a fairly coherent personal history, but without richness of details. She became more interested in her personal appearance and it was possible to schedule visits home. Despite her improvement she did not have a better understanding of her illness or the reasons for being hospitalized.

D.K. (Schizophrenic reaction, Hebephrenic type; maximum tolerated dose = 400 mg; length of hospitalization 10 years). This 44-year-old female presented exuberant symptomatology consisting of delusional ideas and hallucinations. She asserted that she had been born a male but was castrated early in life. She supposedly saw Jesus Christ's dead body and the faces of white men turning black. She heard imaginary talk. These ideas were expressed spontaneously during the interviews and verbalized aloud around the ward.

After medication the patient seemed to be more at ease. She no longer acted as if she were hallucinating and became more interested in her surroundings. She was then able to give a coherent account of her past life. Nevertheless, it was still possible to elicit delusional ideas and hallucinations during the psychiatric interviews.

J.P. (Schizophrenic reaction, Hebephrenic type; maximum dose = 800 mg; length of hospitalization 3 years; history of illness 10 years). The speech of this 26-year-old female was full of bizarre expressions and difficult to understand. She reported visual and auditory hallucinations.

After therapy her speech became understandable and she was able to give an account of her past life. Her personal appearance had improved but careful examination still revealed auditory hallucinations.

S.P. (Schizophrenic reaction, Paranoid type; maximum tolerated dose 400 mg; length of hospitalization 5 years). This 43-year-old female spoke in a rambling way about an atomic force which blew her body to pieces, someone supposedly putting the pieces back together, and the idea that her body belonged to someone else in the past.

After treatment she became quite interested in her family and wrote several letters in an attempt to establish contact with them. She gave a good account of her past life and her speech was no longer rambling. However, careful examination revealed that the patient was still delusional and had hallucinatory experiences.

M.A. (Schizophrenic reaction, Paranoid type; maximum tolerated dose = 400 mg; length of hospitalization 10 years). This 47-year-old

female claimed to be able to see Jesus Christ and supposedly earned $ 60.000 a month. She said she could destroy people by just talking to them and came to the hospital because "There was a strike on the land. It was like a wave. It went through you and if other people talked it would shoot like an explosion."

After treatment she expressed her thoughts more clearly. She no longer expressed delusional ideas spontaneously although they could still be elicited.

F.S. (Schizophrenic reaction, Paranoid type; maximum dose = 800 mg; length of hospitalization 7 years). This 37-year-old female walked around on the ward with her dress pulled between her legs acting as if she were modeling bathing suits. She also decorated herself with bizarre necklaces and bright colored scarfs. She expressed the idea that she lived in Germany rather than in a psychiatric hospital.

After treatment she became quite interested in her family and resumed correspondence with them. She expressed a strong desire to leave the hospital and rejoin her relatives. She was more sociable on the ward, but her delusional ideas and bizarre attire were little modified.

Phenobarbital treated patients. E.A. (Schizophrenic reaction, Hebephrenic type; maximum dose 480 mg; length of hospitalization 16 years). The speech of this 47-year-old female was often incoherent. She expressed numerous persecutory delusions such as a thought that the psychiatrist was going to scalp her. She also claimed to be able to predict the future.

During treatment she was able to communicate better, but her delusional ideas and hallucinations were still present.

I.C. (Schizophrenic reaction, Paranoid type; maximum tolerated dose 480 mg; length of hospitalization 13 years). This 36-year-old female spent a good deal of her time grimacing and talking to herself. She refused to come to the examiner's office despite encouragement to do so.

After treatment she became cooperative and came willingly to the office. She seemed more interested in her surroundings and made attempts to socialize with the ward personnel. Yet, during interviews she was evasive and little information about her past could be obtained.

Results of ranking degree of change. The psychiatrist, using information from the psychiatric examinations and his observations on ward rounds, ranked all patients by degree of overall improvement. Patients who showed more improvement were placed in the higher ranks (1, 2, 3, ...) and those who showed little or no improvement in the lower ranks (..., 55, 56, 57).

The same ranking procedure based on ward behavior was independently done by the ward personnel. A high degree of agreement in

rankings between the psychiatrist and the ward personnel was found, $\varrho = .77$ (Spearman rank correlation coefficient). Although the psychiatrist and the ward personnel provided their rankings independently, to some extent they were working from a common fund of knowledge and observation. It was necessary in ward administration and ward rounds for the psychiatrist and the ward personnel to exchange information concerning patients. In addition to the common information the psychiatrist had the benefit of his periodic psychiatric examinations and the ward personnel had the benefit of close contact with the patients.

When the drug code became available the high, middle, and low thirds of the ranked patients were classified by drug groups (Table 5). The chlorpromazine patients fell primarily in the upper third of the distribution of ranks, the phenobarbital patients in the middle third, and the placebo patients in the lower third. An overall analysis of the table yielded a χ^2 which was significant beyond the .001 level of probability for both the aides' and psychiatrist's rankings.

Table 5. *Distribution by drug groups of rankings by psychiatrist and psychiatric aides*

Distribution of ranks	Psychiatrist			Aides		
	CPZ	Barb.	Plac.	CPZ	Barb.	Plac.
Upper Third .	14	4	1	16	3	0
Middle Third .	5	9	5	3	12	4
Lower Third .	0	6	13	0	4	15
	d.f. = 4, $\chi^2 = 29.7$, $p < .001$			$\chi^2 = 49.60$, $p < .001$		

CPZ = Chlorpromazine, Barb. = Phenobarbital, Plac. = Placebo.

Psychological tests and rating scales

Although monthly evaluations were taken with many measures the data analysis in this paper will be restricted to comparisons at "baseline" (8th week) and "maximum treatment" (24th week) periods. The significance of initial differences between the three drug groups was tested by analysis of variance using the data from the 8th (placebo) week. There was no significant difference between groups on any measure. Analysis of covariance at the 24th week using baseline scores as the covariate are summarized in Table 6. Where warranted, the significance of differences between adjusted means of sub-groups were analyzed by a multiple range test described by SNEDECOR (1959, p. 253), and are summarized in Table 7.

Effects of chlorpromazine. The adjusted means of the chlorpromazine group were significantly different from those of the placebo group at the time of maximum treatment (24th week) on several variables. In

Table 6. *Analysis of variance at peak dose (Fy) and covariance (Fa) using placebo baseline scores as covariate*

Source	d.f.	SSx	SP	SSy	MSy	Fy	Residual			
							SSa	d.f.	MSa	Fa
Purdue Peg Board (I)										
Triplets	18	15150	10863	9445						
Drugs	2	472	941	2370	1185.0	3.526	1288	2	638.5	3.900
Error	36	13647	9322	12096	336.0	(.05)	5729	35	163.7	(.05)
Purdue Peg Board (II)										
Triplets	18	17004	13098	12149						
Drugs	2	493	334	1997	998.5	2.868	1771	2	885.5	6.078
Error	36	15768	10825	12531	348.1	(ns)	5099	35	145.7	(.01)
Digit Symbols										
Triplets	18	5266	3896	4247						
Drugs	2	59	214	1008	504.0	4.071	705	2	352.5	8.066
Error	36	4841	3764	4455	123.8	(.05)	1529	35	43.7	(.005)
Names Known										
Triplets	18	90143	99477	123704						
Drugs	2	955	2220	6022	3011.0	4.618	3749	2	1874.5	6.592
Error	36	42228	23902	23481	652.2	(.05)	9952	35	284.3	(.005)
Time Estimation										
Triplets	18	217426	150509	179243						
Drugs	2	9748	12762	27339	13669.5	1.718	14252	2	7126.0	1.737
Error	36	297165	206035	286451	7957.0	(ns)	143600	35	4102.0	(ns)
"P" (Psychologists' Scale total deviation)										
Triplets	18	3741	2967	2829						
Drugs	2	1	−6	193	96.5	1.965	200	2	100.0	2.667
Error	36	1719	881	1766	49.1	(ns)	1314	35	37.5	(ns)
"P+"										
Triplets	18	1751	1138	1362						
Drugs	2	31	−118	640	320.0	5.424	720	2	360.0	7.059
Error	36	2841	980	2124	59.0	(.01)	1786	35	51.0	(.005)
"P−"										
Triplets	18	3385	3279	3500						
Drugs	2	33	−43	131	65.5	1.835	165	2	82.5	2.874
Error	36	2147	777	1284	35.7	(ns)	1003	35	28.7	(ns)
"TB" (Typical Behavior, Ward Behavior Scale)										
Triplets	18	3401	2313	1949						
Drugs	2	197	286	472	236.0	7.554	312	2	156.0	5.887
Error	36	3648	720	1125	31.2	(.005)	929	35	26.5	(.01)
"TB+"										
Triplets	18	1677	892	961						
Drugs	2	228	364	624	312.0	6.253	193	2	96.5	3.444
Error	36	1539	1120	1796	49.9	(.005)	981	35	28.0	(.05)

Table 6 (Continued)

Source	d.f.	SSx	SP	SSy	MSy	Fy	Residual			
							SSa	d.f.	MSa	Fa
				"TB−"						
Triplets	18	4425	2859	2384						
Drugs	2	2	7	25	12.5	—	19	2	9.5	—
Error	36	2259	1011	1715	47.6	(ns)	1263	35	35.3	(ns)
				"EB" (Extreme Behavior, Ward Behavior Scale)						
Triplets	18	10533	5257	3834						
Drugs	2	293	761	2234	1117.0	8.481	638	2	319.0	3.564
Error	36	5549	2985	4740	131.7	(.005)	3134	35	89.5	(.05)
				"EB+"						
Triplets	18	7133	2713	1728						
Drugs	2	228	401	3343	1671.5	9.743	2894	2	1447.0	11.174
Error	36	3694	2464	6178	171.6	(.001)	4534	35	129.5	(.001)
				"EB−"						
Triplets	18	17963	10637	6925						
Drugs	2	91	38	116	58.0	—	101	2	50.5	—
Error	36	5114	2412	5241	145.6	(ns)	4103	35	117.2	(ns)
				"BV" (Variability of Behavior)						
Triplets	18	3817	773	1502						
Drugs	2	77	−266	2696	1348.0	13.521	2703	2	1351.5	13.211
Error	36	3364	183	3588	99.7	(.001)	3579	35	102.3	(.001)
				Drawing Completion Test (Total Score)						
Triplets	18	8944	5062	6173						
Drugs	2	152	−128	134	67.0	—	315	2	157.5	1.005
Error	36	15026	8153	9909	275.2	(ns)	5485	35	156.7	(ns)
				Attendance at Off-Ward Activities						
Triplets	18	5504	5667	8384						
Drugs	2	115	437	2604	1302.0	4.889	1956	2	978.0	6.210
Error	36	6334	5082	9589	266.3	(.025)	5512	35	157.5	(.01)

Note: x = placebo baseline (8th week) values, y = peak dose (24th week) values, and a = peak dose values after adjustment by covariance. Probability levels are shown in parentheses under each F value.

each case the difference was in the direction of improvement in the chlorpromazine group. Those measures in which there were significant differences between the chlorpromazine and placebo groups were: Purdue Peg Board I and II and Digit Symbols (psychomotor and intellectual effectiveness); "TB", "EB", and "BV" (gross behavioral pathology); "P +", "TB +", and "EB +" (aggression and overactivity); "Names Known" (social awareness); and "Attendance at Off-Ward Activities" (spontaneous participation in daily activities).

No significant differences were found between the adjusted mean scores of the chlorpromazine and placebo groups on the following

Table 7. *Analyses of differences between sub-groups using sequential criteria for .05 level of probability*

Variable	Adjusted means Peak dose Group Mean	Differences between means and (Difference required for significance)		
		CPZ–Plac.	CPZ–Barb.	Barb.–Plac.
Purdue Peg Board (I)	CPZ 44.67 Barb 34.12 Plac 34.61	10.06* (8.50)	10.55* (10.24)	0.49 (8.50)
Purdue Peg Board (II)	CPZ 47.71 Barb 34.31 Plac 38.63	9.06* (8.01)	13.38* (9.67)	4.32 (8.01)
Digit Symbols	CPZ 18.50 Barb 10.73 Plac 11.29	7.21* (4.37)	7.77* (5.26)	0.56 (4.37)
"TB" Typical Behavior pathology	CPZ 21.90 Barb 24.63 Plac 27.79	5.89* (4.15)	2.73 (3.44)	3.16 (3.44)
"TB+" Typical overactivity	CPZ 3.00 Barb 5.02 Plac 7.72	4.72* (4.35)	2.02 (3.61)	2.70 (3.61)
"EB" Extreme Behavior pathology	CPZ 46.70 Barb 54.32 Plac 59.09	12.38* (7.55)	7.62* (6.27)	4.77 (6.27)
"EB+" Extreme overactivity	CPZ 6.24 Barb 18.52 Plac 23.17	16.93* (9.17)	12.28* (7.61)	4.65 (7.61)
"BV" Variability of Behavior	CPZ 14.07 Barb 25.68 Plac 30.56	16.49* (8.07)	11.61* (6.70)	4.88 (6.70)
"P+" Overactivity Psychologists' Scale	CPZ 0.98 Barb 6.49 Plac 9.62	8.63* (5.68)	5.51* (4.71)	3.12 (4.71)
"Names Known"	CPZ 38.94 Barb 19.12 Plac 26.51	12.43* (11.23)	19.82* (13.53)	7.39 (11.23)
"Attendance at Off-Ward Activities"	CPZ 19.56 Barb 6.07 Plac 8.37	11.19* (8.29)	13.49* (10.00)	2.30 (8.29)

CPZ = Chlorpromazine, Barb = Phenobarbital, Plac = Placebo; differences greater than expected at .05 probability are designated *.

measures: All aspects of the Drawing Completion Test; Time Estimation; "P" (gross overall pathology on Psychologist's Scale); "P−", "TB−", and "EB−" (underactivity and withdrawal).

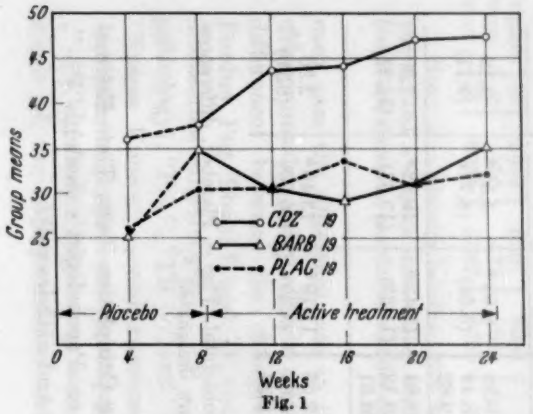

Fig. 1

Fig. 1. Purdue Peg Board (I) scores for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 2. Digit Symbols scores for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 3. Names Known scores for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 4. "P +" (Psychologists' Scale) plus scores for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

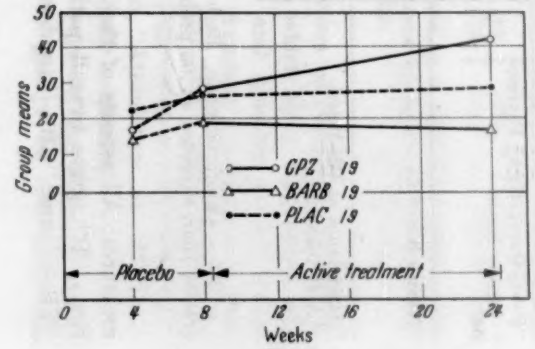

Fig. 3

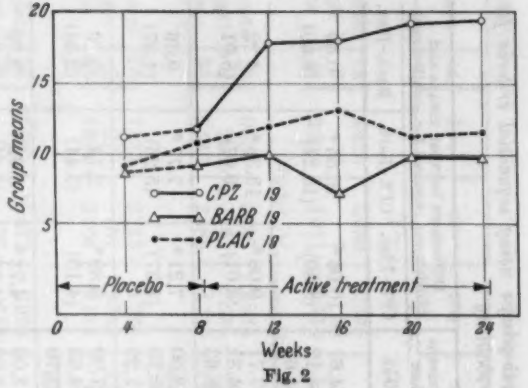

Fig. 2

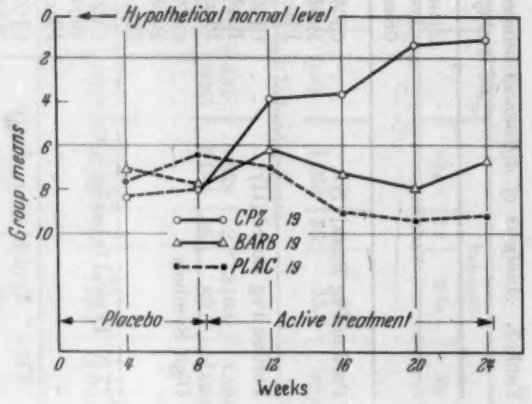

Fig. 4

Effects of phenobarbital. There were no significant differences between the adjusted means of the phenobarbital and placebo treated groups at the time of maximum treatment (24th week).

Comparison of chlorpromazine and phenobarbital. Comparisons between chlorpromazine and phenobarbital adjusted means produced statistically significant differences between the following measures: Purdue Peg Board I and II and Digit Symbols; "EB" and "BV"; "EB +" and "P +"; "Names Known"; and "Attendance at Off-Ward Activities." In all cases the chlorpromazine scores were superior to the phenobarbital scores.

There were two variables in which the chlorpromazine and pheno-

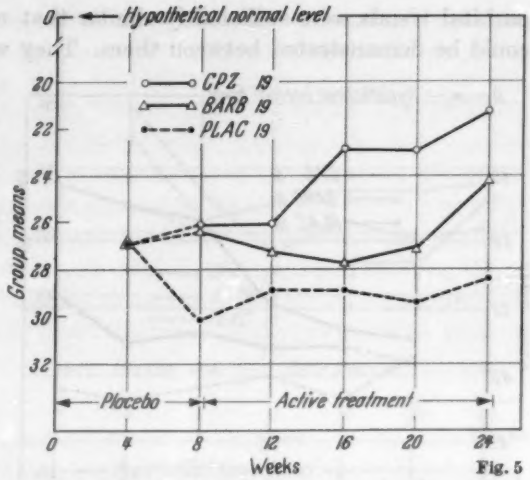

Fig. 5

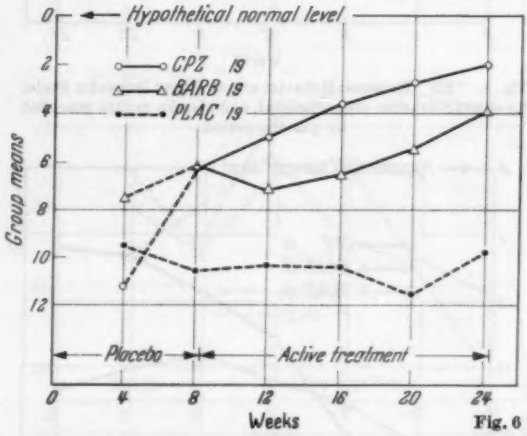

Fig. 6

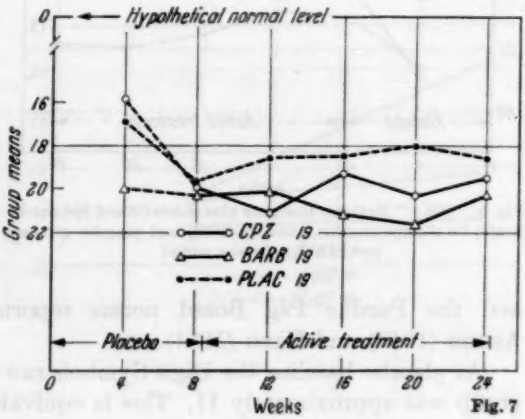

Fig. 7

Fig. 5. "TB" Typical Behavior scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 6. "TB +" Typical Behavior plus scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 7. "TB −" Typical Behavior minus scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

barbital trends were sufficiently similar that no significant differences could be demonstrated between them. They were: "TB" and "TB+" of the behavior scale. For each of these measures chlorpromazine continued to maintain a trend toward superiority in the reduction of behavioral pathology.

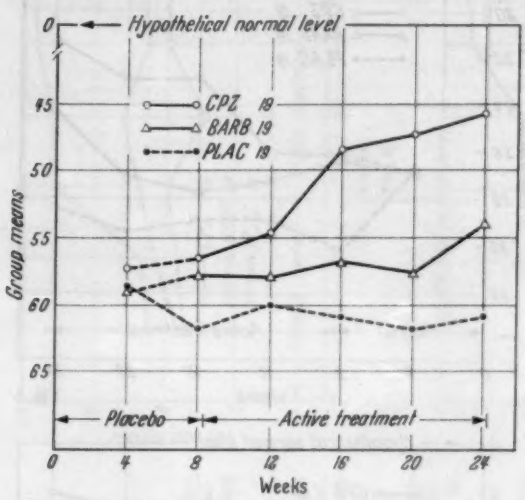

Fig. 8. "EB" Extreme Behavior scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

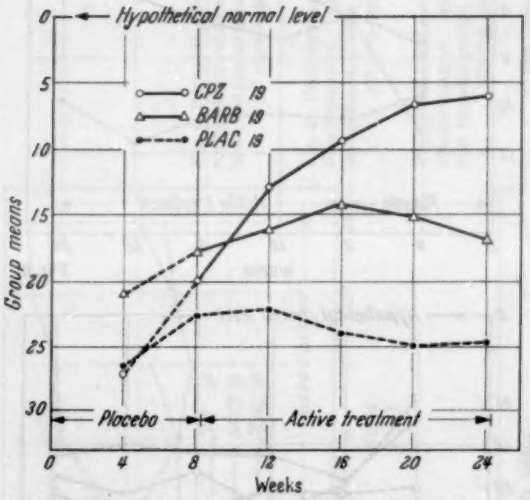

Fig. 9. "EB+" Extreme Behavior plus scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

The data trends through successive monthly measures are presented in Figs. 1 through 12. Group means, in these figures, were adjusted to a marginal scale which extends approximately ± 4 standard errors of the mean when $n = 19$. Thus, the significance of graphic variations are approximately equal from figure to figure. The group means are plotted for each date on which the particular measure was taken, generally each 4 weeks. Statistical analysis of the intermediate and follow-up data will be presented in another paper.

Comparison with normative data. Performance of patients was compared with normative data reported in the test manual for the WAIS Digit Symbols and the Purdue Peg Board norms reported by both TIFFIN and ASHER (1948) and KING (1954).

At placebo baseline the Digit Symbols raw score mean of the patient group was approximately 11. This is equivalent to a scaled score of 3

in the 35—44 year age range in which the mean scaled score is 10. At the point of greatest improvement the chlorpromazine group mean was approximately 19 which is equivalent to a scaled score of 5 in the same age group (Fig. 2). Thus, even at the highest scoring level the patients were considerably below the expected mean for the nonpatient standardization group.

The mean Purdue Peg Board values described by TIFFIN and ASHER (1948) for Industrial Women are equivalent to a total pegs score of approximately 84. At placebo baseline the Purdue Peg Board mean of the patients was approximately 35 which is less than what is given as the lowest percentile for the standardization group. At the point of greatest improvement the chlor-

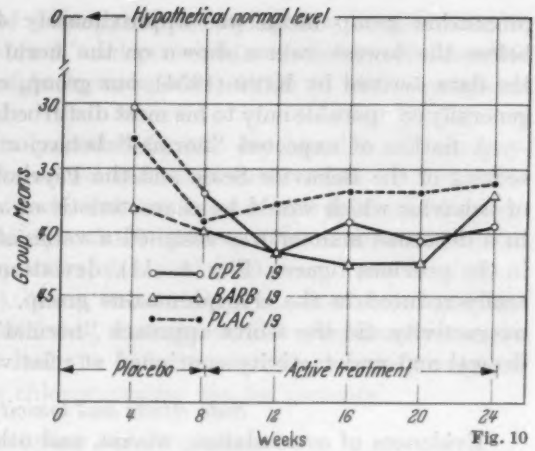

Fig. 10

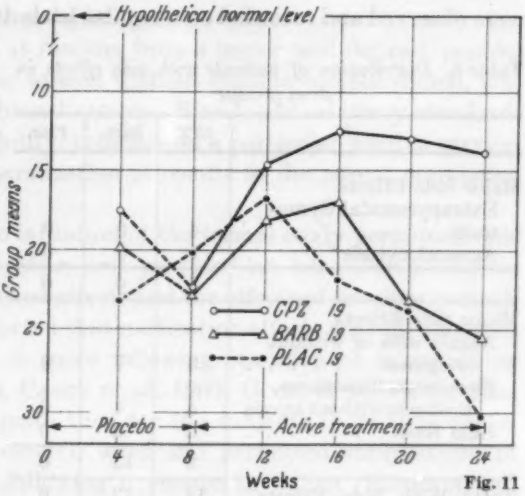

Fig. 11

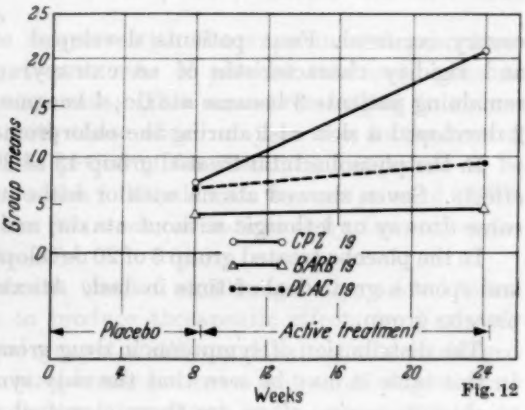

Fig. 12

Fig. 10. "EB —" Extreme Behavior minus scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 11. "BV" Variability of Behavior scores (Ward Behavior Scale) for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

Fig. 12. Attendance at Off-Ward Activities for chlorpromazine, phenobarbital, and placebo groups preceded by placebo period

promazine group mean was approximately 47 which (Fig. 1) is still below the lowest values shown on the norm tables. Compared with the data derived by KING (1954), our group, even at its best level, was generally comparable only to his most disturbed chronic group of patients.

A notion of expected "normal" behavior has been built into the scoring of the Behavior Scale and the Psychologists' Scale. That level of behavior which would be characteristic of a normal person behaving in a decorous manner was assigned a value of "zero." As can be seen in the previous figures (Figs. 4—11), deviations from "zero" were generally reduced in the chlorpromazine group. Only in the reduction of overactivity did the scores approach "normal" levels. Indices of withdrawal and underactivity continued at relatively deviant levels.

Side effects and toxicity

Evidences of oversedation, ataxia, and other nontherapeutic effects were observed and recorded on a regular basis during the ward rounds and in conjunction with periodic taking of temperature and blood pressure. In the chlorpromazine treated group 14 of 20 patients evidenced sideeffects. One patient developed agranulocytosis in the twelfth week of chlorpromazine treatment at the 800 mg daily dose level. This patient was withdrawn from the study and transferred to the medical service where recovery occurred. Four patients developed masklike facies, drooling, and rigidity characteristic of an extrapyramidal syndrome. Of the remaining patients 3 became ataxic; 4 became drowsy or lethargic; and 2 developed a skin rash during the chlorpromazine treatment.

Table 8. *Distribution of patients with side effects in drug groups*

	CPZ	Barb.	Plac.
Major Side Effects			
Extrapyramidal Symptoms	4	0	0
Agranulocytosis	1	0	0
	5	0	0
Minor Side Effects			
Ataxia with or without sleepiness	3	7	0
Sleepiness, drowsiness, tiredness without ataxia	4	4	6
Skin Rash	2	2	0
	9	13	6
Total With Side Effects	14	13	6

In the phenobarbital treated group 13 of 20 patients developed sideeffects. Seven showed ataxia with or without apparent sedation, 4 became drowsy or lethargic without ataxia, and 2 developed a skin rash.

In the placebo treated group 6 of 20 developed drowsiness or sleepiness and spent a great deal of time in bed. Ataxia was not observed in the placebo group.

The distribution of symptoms in drug groups is presented in Table 8. In this table it may be seen that the only symptoms which are specific to chlorpromazine alone are those classified as major side-effects.

Since the presence of extrapyramidal symptoms might serve to compromise the "double-blind" and permit bias in the results, the data for the 4 patients who might have been identified by these symptoms were separately examined.

Using the ranked data provided by the psychiatrist and the psychiatric aides it was determined that the mean ranks of the chlorpromazine treated patients who did not develop extrapyramidal symptoms were 10.4 (Psychiatrist) and 9.7 (Aides). The mean ranks of the patients who did develop extrapyramidal symptoms were 24.5 (Psychiatrist) and 23.8 (Aides). Thus, those chlorpromazine treated patients who could have been identified by extrapyramidal symptoms were seen by both the psychiatrist and the aides as showing less improvement than the remainder of the chlorpromazine treated patients.

Discussion and conclusions

Methodological considerations

The subjects, selected at random from a larger well-defined population (chronic schizophrenic women without organic complications), presumably constitute an unbiased sample. Bias due to arbitrary standards of cooperativeness, availability, presence on a particular ward or service, etc., was avoided and generalization of results to the parent population should be permissible.

The 13 months prior to initiation of the formal study permitted slow withdrawal of prior medication and provided an adequate period for dissipation of prior medication effects and the effects of previous somatic therapies. It has been reported that medication effects are still apparent for as long as 3 months or more following cessation of tranquilizing therapy (Rothstein 1960, Casey et al. 1960, Good et al. 1958). This period also provided adequate time for the subjects to become accustomed to living on the research ward and permitted stabilization of effects which may occur following a change in milieu (Rashkis and Smarr 1957).

Familiarization of the subjects with the experimental procedures was accomplished during two months of placebo treatment prior to treatment with active compounds. This maneuver helped to reduce confusion of drug effects with those which may be due to the testing and treatment routine. This period of familiarization appeared to be adequate since the changes which followed, with the exception of "BV", tended to stabilize after the 8th week, as indicated by the curves for the placebo group (Figs. 1—12).

The dose of chlorpromazine was set at 800 mg daily, a level found to be generally adequate to produce therapeutic effects by Freeman et al. (1956). Phenobarbital was set at 480 mg daily, an amount judged to be an effective dose in schizophrenic patients. Individual adjustments downward from these levels were permitted in the event of toxicity

only. By this procedure individuals whose tolerance for the medications was less than the prescribed level were permitted to continue in this study at their individually tolerated doses. Throughout the experiment only one patient was lost from the study (agranulocytosis). The data of each other member of that triplet were deleted from the other two groups before statistical analysis in order to preserve the balance of the groups. Maintaining all other subjects at their individually tolerated doses served to avoid a high toxicity attrition rate and to preserve the representativeness of the sample.

Two methods were used to control the effect of initial individual differences. Treatment groups were matched on the basis of Behavior Scale ratings obtained prior to treatment by selecting matched triplets and randomly assigning one member of each triplet to each treatment group (randomized complete blocks design). Although, after this procedure, no significant differences between groups were found on any pre-treatment measures, further statistical control was applied through use of analysis of covariance with initial scores as the covariate for each variable analyzed. It may be noted that, with the exception of Peg Board II, the refinement attained through the use of covariance did not alter the basis for statistical decisions otherwise provided by the simple (unadjusted) analysis of variance (Table 6).

Although various toxic manifestations were observed in all three groups, extrapyramidal symptoms were distinctive to the chlorpromazine group. However, analysis of the data obtained through ranking procedures, a method which is very susceptible to personal bias, suggests that these distinctive symptoms did not bias these results in favor of chlorpromazine.

The measures and observations of treatment effects were independently derived from three sources: Judgments and observations by the psychiatrist; judgments and scaled behavioral observations by ward personnel; and tests and scaled observations by the psychologists. These simultaneous observations on several facets of functioning of the whole person may be considered separately or together.

Interpretation of results

Psychiatric and clinical observations. The observations of the psychiatrist, which provide a more global view of the drug effects and bear directly on the question of clinical efficacy, revealed that only 6 chlorpromazine treated patients appeared to manifest clinically significant improvements compared with 2 in the phenobarbital group and none in the placebo group. Changes of a more subtle nature and of a degree that failed to meet the psychiatrist's standards for clinically significant improvement were nonetheless observable and were brought out in the ranking procedure.

Among those subjects who were more clearly improved the changes manifested themselves in the psychiatric examination by improved ability to communicate and diminution of severity of symptoms. There was also a lessening of subjective anguish and discomfort as psychotic productions became less frightening to the patients. On the ward these patients were observed to become more interested in others and their surroundings. They engaged in fewer excesses in behavior and became more manageable. In each case, however, the patients continued to manifest fairly obvious symptoms of schizophrenia. The improvements shown were only a partial reduction of symptoms but were sometimes striking and important.

Behavior scale, ward records, and rankings by ward personnel. a) The effects of chlorpromazine on behavior are reflected primarily in the curtailment of agressiveness or overactivity as well as a relative reduction in excessive swings in behavior. Similar but nonsignificant trends in the reduction of overactivity were seen in the phenobarbital group. Inspection of the behavior scale revealed that the ratings of chlorpromazine treated patients tended to converge at a somewhat subdued level of behavior on several items. This will be discussed in detail in a subsequent report.

b) Degrees of improvement judged by the ranking procedure of the ward personnel favored chlorpromazine, phenobarbital, and placebo in that order. Although in their rankings, ward personnel used a subjective set of values which were oriented toward the well-being of patients, there can be little doubt that ward manageability entered into the decisions.

Psychological tests and ratings. a) Ratings of level of participation and behavior during the psychological examinations agree essentially with the general findings of the Behavior Scale used in the ward. Underactivity and withdrawal were unaffected, but significant reductions in overactivity or outgoing behavior (P +) were found in the chlorpromazine group.

b) Drawing Completion Test and Time Estimation were the only tests which failed completely to reflect a significant drug effect. The scores on DCT were highly stable and did not vary significantly with treatments. The Time Estimation scores were very unstable and any effects which might have been present were masked by extreme variability. The data trends, however, were consistent with other data in which chlorpromazine was superior.

c) Significant improvements in psychomotor effectiveness (Purdue Peg Board) were found in the chlorpromazine group when contrasted with the other two groups, although improved levels of performance were still inferior to normative data. This finding should be interpreted in light of the fact that when used with this class of patients the Purdue

Peg Board appears to require a certain level of attention, motivation, and freedom from confusion as well as manual dexterity. Increases in scores should not be interpreted as improvement in manipulative dexterity alone. Although this is the medium through which the effects of the treatments were expressed, handicapping on the test did not always seem to be due primarily to a lack of manual facility but often involved inefficiency associated with mental and emotional factors.

d) Significant improvements in intellectual effectiveness (Digit Symbols) were found in the chlorpromazine group when contrasted with the other two groups. As in the case of peg board scores, this finding should be interpreted in the light of the class of patients involved. Performance deficits seemed most often clearly associated with mental and emotional factors such as compulsiveness, confusion, and inattention, which are prevalent among chronic schizophrenic patients.

e) A significant increase in awareness of others was found in the chlorpromazine group compared with the other groups. The "Names Known" procedure was employed to study the extent to which the patients were aware of and could recall the names of one another. Responses undoubtedly reflect to some degree the motivation and willingness of patients to cooperate with the examiner by answering questions, as well as immediate memory and clarity of thought. However, to some extent it is also related to "persons known" and as such is a reflection of social awareness.

This procedure was followed by the standard sociometric questions "Who do you like best ?" and "Who do you like least ?". Our experiences were similar to those of TOURLENTES et al. (1958), in that our patients resisted stating negative preferences to a very marked degree. Surprisingly, however, they resisted stating positive preference to the degree that these data were also unusable. Indeed, some reluctance was expressed in the naming of others even without the evaluative implications.

Synthesis of findings

While appearing to inhibit several aspects of psychopathology and pathological behavior in these chronic schizophrenic subjects, chlorpromazine therapy apparently increased the effectiveness of mental activity and facilitated a more effective channeling of daily behavior into sociable activities. Its overall effect was toward relatively better integration and organization of the whole person.

This is in contrast to the sedative, phenobarbital, which produced only nonsignificant trends toward subdued behavior in matched subjects.

However, not all patients responded in the described manner to chlorpromazine. Although roughly $^1/_3$ of the subjects evidenced improvements in all 3 general areas of evaluation, some patients improved only in a limited or isolated way, and others did not appear to change

at all. Only 6 of 19 subjects were considered to be improved to a clinically significant degree by the psychiatrist and none of these patients were changed sufficiently to be considered fully recovered or ready for discharge. The fact that improvement on chlorpromazine is only partial is further reflected in the general scoring levels of the patients on psychological tests which did not attain the level of normative groups.

It is apparent that chlorpromazine can produce statistically significant effects in several areas of functioning in chronic schizophrenic women. However, from a clinical viewpoint and by comparison with normative standards of performance, its effectiveness is relatively limited. From the standpoint of research it may be seen as a valuable tool for manipulating the psychological functioning of chronic schizophrenic patients.

Summary

The effects of chlorpromazine and phenobarbital were studied in a randomly selected group of 60 chronic schizophrenic women by an interdisciplinary research team. Patients were matched and randomly assigned into three treatment groups. Following 8 weeks of placebo, maximum daily doses of 800 mg chlorpromazine, 480 mg phenobarbital, and an equal number of identical placebos were administered "double-blind" over a 16-week period. Multiple criteria of treatment effects included psychiatric examinations, psychological tests, a new ward behavior scale, and ward records. Tests and scales were administered each 4 weeks while the psychiatric examinations were conducted at the beginning and end of the study. Ranked data were grouped and analyzed by χ^2 and measurement data were analyzed in a randomized blocks design by analysis of variance and covariance.

Chlorpromazine treated patients became more subdued and more stable in daily ward behavior while spontaneously participating to a greater extent in off-ward activities. Intellectual and psychomotor effectiveness increased and the patients became more interested in their surroundings and aware of one another. Psychopathology was diminished although none of the patients were completely free of symptoms and none were considered for release from the hospital. The overall activity of chlorpromazine, though limited, was toward better organization and integration of the individual. The extent to which these effects were manifest from one subject to the next was variable and a number of subjects failed to respond to chlorpromazine.

While significant chlorpromazine effects were found in all major areas of evaluation, it failed to produce significant effects on time estimation, the Drawing Completion Test, and the withdrawn or underactive aspects of behavior measured by the behavior scale and the psychologists' scaled ratings. No significant effects of phenobarbital were found.

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Short Communications · Kurze Originalmitteilungen
Communications brèves

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The Effects of Promazine on MMPI Performance in the Chronic Psychiatric Patient* **

By
EDWARD S. SULZER

(Received May 27, 1960)

The general hypothesis underlying this study was that if the ataractic drugs improve the clinical picture presented by young chronic, hospitalized psychiatric subjects, predictable changes should be evident on standardized structured personality assessment techniques. Promazine[1] was the drug investigated and the Minnesota Multiphasic Personality Inventory (MMPI) (HATHAWAY and MCKINLEY 1951) was the device used to assess changes. The MMPI was selected as several previous studies report that it may indicate change concomitant with other forms of psychiatric treatment (CARP 1950, DANA 1957, FELDMAN 1952, GALLAGHER 1953, HALES and WERNER 1948, KAUFMAN 1950, RASHKES and SHASKIN 1946, SCHOFIELD 1950, 1953, WEST 1953, WINTER and FREDRICKSON 1956). The MMPI appears to be a relatively stable measure of significant personality attributes (DAHLSTROM and WELSH 1960, pp. 472—474).

Methods

The subjects were 41 male patients 45 years of age or younger, who had been diagnosed as schizophrenic for at least one year, and who had shown no significant clinical indications of improvement during hospitalization. None had any major secondary diagnosis of significant physical disease. Twenty-nine of the subjects were in group psychotherapy throughout the study and the remaining 12 were not given any active treatment other than the promazine.

For the initial four weeks of the study, all subjects were given a placebo capsule identical in appearance to the promazine capsule. The

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** A report of the results of this research was delivered at the Eastern Psychological Association meeting, April, 1959, in Atlantic City, New Jersey.

[1] Sparine, Wyeth.

medication or placebo was distributed to the patients by staff members who were unaware of the contents of the capsules.

Following this period, 13 of the patients in group therapy and five not in group therapy were administered promazine 400 mgs a day for 45 days. The remaining 23 patients were kept on placebo. The situation was then reversed and the 18 patients on promazine were returned to the placebo. At the same time, the 16 patients in group therapy and the seven not in group therapy who had been given only placebos were put on promazine for a period of 43 days.

Table. *Mean raw scores of MMPI scales for drug and placebo periods. Total group of subjects—N=41*

MMPI Scale	Placebo Mean	Drug Mean
?	6.1	4.2
L	6.2	6.8
F	17.8	18.8
K	16.1	16.8
Hs	10.9	11.9
Hs+.5K	19.2	20.5
D	26.5	27.0
Hy	25.0	26.8
Pd	21.1	21.8
Pd+.4K	27.6	28.6
Mf	26.9	27.5
Pa	15.7	16.2
Pt	18.5	17.8
Pt+1K	34.8	34.5
Sc	26.3	26.8
Sc+1K	42.4	43.4
Ma	20.4	21.3
Ma+.2K	23.5	24.6
Si	30.9	31.1
Es (BARRON)	38.6	37.5
MAS (TAYLOR)	18.5	17.7

During the final stage of the study, all patients were administered placebos for 34 days. After each of the aforementioned four periods, the MMPI was administered to each patient. A few of the patients were unable to undertake the MMPI successfully on all four occasions, but they were included in the final analysis if there were at least 2 placebo MMPI's (one pre-drug and one post-drug) and the one active drug MMPI.

The final data were analyzed by taking the means of the placebo MMPI scale scores for each of the four subgroups of patients and comparing them with the promazine scale scores. Then, the total group means were computed for the placebo periods and compared to the total mean scores of the drug periods. The statistic used was the *t* test for differences in arithmetic means. A *t* at the .05 level was required for statistical significance. The predictions tested were that each scale would reflect an improved clinical picture such that deviations from the standard population means would be reduced.

All the usual validity and clinical scales (?, L, F, K, Hs, D, Hy, Pd, Mf, Pa, Pt, Sc, Ma, and Si) were scored with and without the K corrections recommended by the authors of the inventory for the Hs, Pd, Pt, Sc, and Ma scales (HATHAWAY and MCKINLEY 1951). In addition, the Manifest Anxiety Scale (TAYLOR 1951, TAYLOR 1953) and the Ego-Strength (BARRON 1953) scale were scored.

Results

The results did not reveal any significant difference between the means of the placebo periods and the drug period for any of the four sub-groups of patients or for the total patient group. The Table reports the means of the placebo and drug periods for each of the scales on the entire patient sample.

Discussion

These findings suggest several alternative explanations. First, the drug may have had a significant effect on the subjects but the MMPI may not be sufficiently sensitive in the appropriate areas to detect the changes. Second, the drug may not have produced significant alterations in the behavior of the patients. If the latter is, in fact, the case, then consideration must be given to such other variables as drug dosage, type of patients, suitability of promazine as compared to other ataractics, length of medication period, or other factors that would inhibit or enhance drug effect with chronic schizophrenic patients. Probably the fixed nature of the dosage requires further examination. It may be that had individual dosage been determined via clinical assessment, weight, or other factors, changes might have been detected. However, the double-blind nature of the study prevented such a procedure. It is also possible that the amount of promazine might have been on the low side in light of more recent reports on the efficacy of larger dosages.

Summary

A double-blind controlled study of the effects of promazine on MMPI performance is herein reported. The subjects were 41 male hospitalized patients who had been clinically diagnosed as schizophrenic for at leas one year. Twenty-nine of the subjects were concomitantly in grout psychotherapy. All the usual validity and clinical scales, the Taylop Manifest Anxiety Scale, and the Barron Ego-Strength Scale of the MMPr were scored. A comparison of the mean scale scores between the placebI and drug periods revealed no statistically significant differences for ano of the scales. Alternative explanations for these findings are offeredy

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The Measurement of Observed Differences between Treated and Untreated Animals Using an Ordinal Scale for Ranking the Degree of Confidence in their Judgment of two Unbiased Observers

By

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Measurement is the process of mapping or assigning numbers to objects or observations (SIEGEL 1956). The nature of many pharmacological phenomena is such that only a weak level of measurement can be used for studying them. It happens frequently in pharmacology that the objects in one category of a scale stand to the objects in the other categories of that scale in a typical relation which may only be designated by the carat (>). The carat, in general, means "greater than" and its specific meaning depends on the nature of the relation that defines the scale. The distances or ratios between any two numbers on the scale are frequently not of known size. In these instances the nominal or ranking scale represents the highest level of measurement that can be achieved. A typical example is the problem of how to measure visible drug effects on phenomena for which there is no satisfactory ratio scale such as subjective phenomena in man, or behavior aspects in animals.

The purpose of this paper is to describe and to illustrate an ordinal scale which has been extensively used in this laboratory for measuring differences between treated and untreated animals as recorded by the human eye.

Method

Basically, two trained observers are asked to make certain observations in a given experimental condition on a pair of animals, simultaneously and for the same length of time. Both animals are of similar weight, sex, strain and age. Both observers know that one animal has been treated with solvent (control animal) and that the other animal has been treated with a certain amount of chemical substance. The nature of the substance as well as the identity of the treated animal are unknown to the observers. At the end of each period of observation both observers

are required to state independently a preference for one of the animals. The exact meaning of the preference depends on the type of experiment and should be accurately defined. Each observer is also required to use the following nominal scale for ranking the degree of confidence in his judgment or selection.

Score 1. "I did not observe any significant difference between both animals. My preference, therefor, is based on highly subjective criteria of selection."

Score 2. "I did observe a clear difference between both animals. I did not observe any phenomena however which I would regard as 'abnormal' or due to drug action."

Score 3. "I observed a difference between both animals which, in my opinion, was due to drug action."

Observation, selection and ranking are all done independently; the observers are not supposed to communicate with each other in any way during the entire experiment.

In an experiment of this type K observers may successively observe N pairs of animals.

Results

A typical example may be described as follows:

A series of 8 pairs of male Wistar rats of equal strain, age and body-weight are selected. The back of one rat of each pair is painted red ("the red rat" R), the other rat is not painted ("the white rat" W). The rats are then selected at random for injection. One rat of each pair is given a subcutaneous dose of 0.31 mg/kg of chlorpromazine hydrochloride, the other rat being similarly and simultaneously injected with solvent (10 ml of water per kg body-weight). The 8 pairs ($N = 8$), designated n_1 to n_8, are thus treated at intervals of about one minute and put in plastic containers. One hour after injection each pair of rats is taken out of their container by one of the observers and dropped simultaneously into an open top glass cylinder (diameter: 25 cm; height: 25 cm) on a metal plate. Both observers are then allowed to observe the two rats for exactly 30 seconds. At the end of this period each observer, using a standard form (Table I) proceeds as follows:

He indicates the "preferred" rat of each pair, i.e. the rat having shown less general locomotor activity than its partner, by circling the printed letters W (white rat) or R (red rat). He then adds his score (1, 2 or 3) thus expressing his degree of confidence in his judgment, as indicated above. At the end of the whole experiment, the code is broken, and the chlorpromazinetreated rat of each pair is identified by underlining either letter W or letter R. The 16 scores allocated by both observers to the 8 pairs of rats are then given the appropriate sign, a

negative sign being given when the "preferred" rat was actually pretreated with chlorpromazine ("less locomotor activity") and a positive sign if the pretreatment was the solvent.

The final results are given in Table 1.

Table 1. *The influence of chlorpromazine (0.31 mg/kg subc.) on general locomotor activity of rats. (Two observers X and Y: 8 pairs of rats: n_1 to n_8).* Further details are given in the text

Pair	Obs. X		Obs. Y		Scores	
					Obs. X	Obs. Y
n_1	$\underline{W}_1$	R	$\underline{W}_1$	R	−1	−1
n_2	$\underline{W}$	$\underline{R}_1$	$\underline{W}$	$\underline{R}_1$	+1	+1
n_3	$\underline{W}$	$\underline{R}_1$	$\underline{W}_1$	R	+1	−1
n_4	W	$\underline{R}_1$	W	$\underline{R}_1$	−1	−1
n_5	W	$\underline{R}_1$	W	$\underline{R}_1$	−1	−1
n_6	W	$\underline{R}_2$	W	$\underline{R}_1$	−2	−1
n_7	$\underline{W}_1$	R	$\underline{W}_1$	R	−1	−1
n_8	$\underline{W}_1$	R	$\underline{W}_1$	R	−1	−1
				average	−0.625	−0.75

One tailed binomial probabilities under H_0:
— frequency of positive scores: $(P = Q = 1/2)$
for X : $p\,(x \leqq 2) = 0.145$ $(N = 8)$
for Y : $p\,(x \leqq 1) = 0.035$ $(N = 8)$
for $X + Y$: $p\,(x \leqq 3) = 0.011$ $(N = 16)$
— frequency of pairs of scores with opposite sign $(P = Q = 1/2)$
$p\,(x \leqq 1) = 0.035$ $(N = 8)$
— frequency of pairs with different scores $(p = 5/6)$ $p\,(x \leqq 2) < 0.01$

Obviously, the frequency of positive scores (2/8 for X and 1/8 for Y) is very low. The probabilities $p\,(x)$ associated with frequencies as small as the observed frequencies x are given by the binomial test. The proportion of expected positive scores P and the proportion of expected negative scores Q or $1 - P$ are the same $(P = Q = 1/2)$.

The probability of obtaining x positive scores and $N - x$ negative scores is given by the binomial

$$p(x) = \frac{N!}{x!\,(N-x)!}\, p^x Q^{N-x} = \binom{N}{x}\left(\frac{1}{2}\right)^x \cdot \left(\frac{1}{2}\right)^{N-x}$$

and the sampling distribution of the binomial giving the probability of obtaining the observed value of x or values even more extreme is

$$\sum_{i=0}^{x} \binom{N}{i} P^i Q^{N-i} = \sum_{i=0}^{x} \binom{N}{i}\left(\frac{1}{2}\right)^i \left(\frac{1}{2}\right)^{N-i}.$$

The one-tailed probabilities under the null hypothesis H_0 for this binomal ($P = Q = {}^1/_2$; $N = 8$ or 16) are

$N = 8$	$N = 16$
$p(0) = 0.004$	$p(x \leqq 2) = 0.002$
$p(x \leqq 1) = 0.035$	$p(x \leqq 3) = 0.011$
$p(x \leqq 2) = 0.145$	$p(2 \leqq 4) = 0.038$
$p(x \leqq 3) = 0.363$	$p(x \leqq 5) = 0.105$
	$p(x \leqq 6) = 0.227$
	$p(x \leqq 7) = 0.402$

Analysis of the data in table 1 therefor leads to the following conclusions:

1. The concordance between both sets of scores is excellent. The score system was therefor used in a very similar way by both observers. This is shown by the fact that only one pair of scores out of eight has opposite signs ($P = 0.035$) and that six pairs are identical ($P < 0.01$).

2. The chlorpromazine-treated rats (0.31 mg/kg subc.) showed significantly less general locomotor activity than their saline-treated partners. This is shown by the very high frequency of negative scores selected by both observers ($P = 0.011$).

3. In this experiment the effect of chlorpromazine was very small. Only one observer selected score 2 and only once, and no phenomena were observed which were thought to be drug-effects (score 3). The average or mean score (-0.63 for X and -0.75 for Y), although devoid of mathematical meaning, is a useful symbol for "intensity of effect".

Several such experiments with two observers and 8 pairs of rats may be used for investigating the effects of various doses of a particular compound, and the results may be conveniently summarized at shown in Table 2.

We have successfully applied this ordinal scale system for measuring qualitative differences between treated and untreated animals to a variety of pharmacological problems, e. g.:

1. The influence of drugs on the palpebral split of undisturbed rats in a familiar environment (Table 2). The observers are requested to select the animal with the "greatest tendency to close the eyes". Negative scores indicate a tendency to produce ptosis (e.g. neuroleptic drugs) and positive scores a tendency to produce exophthalmia (e. g. amphetamine or morphine). The method was found to be extremely sensitive.

2. The influence of drugs on the reactions of mice or rats to a given noxious stimulus, such as a hot plate, pressure on the tail, pinching the toes, etc. The observers are made familiar with the type of reaction which is commonly seen in control animals and then requested to select the animal of a given pair showing "less" of these reactions than its partner.

Negative scores indicate a tendency of the drug to reduce the intensity of the reactions to the noxious stimulus. Some of these methods will be described in detail in subsequent papers.

Table 2. *The influence of various subcutaneous doses of Haloperidol on palpebral split in Wistar rats (8 pairs of rats per dose level)*

		Observers									
		HG	DF	DF	—	DF	DF	—	HG	HG	
		Mean score									
		−.50	−.88	−1.6	—	−2.9	−2.9	—	−2.8	−2.8	
Frequency of scores	+3										0
	+2										0
	+1	5	3								8
	−1	8	9	10							27
	−2	3	4	2		2	2		3	3	19
	−3			4		14	14		13	13	58
	mpk s. c.	0.02	0.04	0.08	0.16	0.31	0.63	1.25	2.5	5	
	$p\,(x>y)$	0.11	0.011	<0.001	—	<0.001	—	<0.001	<0.001	<0.001	

Frequency

A) of identical pairs of scores: $P=1/6$; $p\,(x\geqq 47)<0.001$; $N=56$ — 47/56 { −3 −3 : 27; −2 −2 : 6; −1 −1 : 11; +1 +1 : 3

B) of pairs of scores with opposite sign: $P=1/2$; $p\,(x\leqq 2)<0.001$; $N=56$ — 2/56 { +1 −1 : 2

C) of non-identical pairs of scores with the same sign: — 7/56 { −1 −2 : 3; −3 : 4

56

Discussion

It should be obvious that the reliability of this technique depends on many factors which should be controlled as much as possible.

The quality of the observer certainly is of the utmost importance. Experience shows however that the concordance among different observers increases as a rule with training and may reach an amazingly high level of significance. In spite of this, the fact remains that certain persons are simply unsuitable for this type of work. Adequate selection of the observers on the basis of the degree of concordance among them, as evaluated by binomial analysis, is therefor of great importance.

Another important source of error is the inadequate formal description of the score system. An adequate description should have as nearly as possible the same meaning to different persons. Whether this is so or not may be found out by actually using a proposed description

and following the significance of the degree of concordance among observers in function of time.

Experience shows that certain descriptions of the score system are "better" than others in this respect. We have found e.g. to our surprise that the term "general motor activity" seems to have very nearly the same meaning to all eight different observers who have had sufficient experience with a test in which this term was used in describing the score system.

Note also that the technique, as described in this paper, is less suitable for studying the effects of drugs on phenomena for which there is considerable variability in control animals (e.g. aggressive behavior in monkeys) than for studying phenomena for which the inherent variability is less. This point should be kept in mind when designing a new experimental application of this general method.

In the examples we have used eight pairs of animals per dose and two observers. These are minima. To increase the number of observers is often impractical and advisable only when the isolated experiment is complicated or expensive. The optimal number of pairs to be used per dose can of course be determined by sequential analysis. This is a matter of practical interest. The observers should decide a priori how much effort they want to spend on the investigation of the effect of any given dose. They should also a priori set a limit to the degree of confidence they want to achieve.

Special care should finally be taken to rule out conscious or unconscious communication between the observers during the experiment. If at all possible the observers should not be aware of the nature of the drugs under investigation. All this in order to avoid possible bias of judgment.

Summary

This paper describes and illustrates a general method for measuring visible difference between treated and untreated animals using an ordinal scale for ranking the degree of confidence in their judgment of two unbiased and independent observers. The method may be successfully used for studying phenomena for which there is no satisfactory ratio scale. Binomial and sequential analysis may be used for evaluating reliability and significance of the drug effects.

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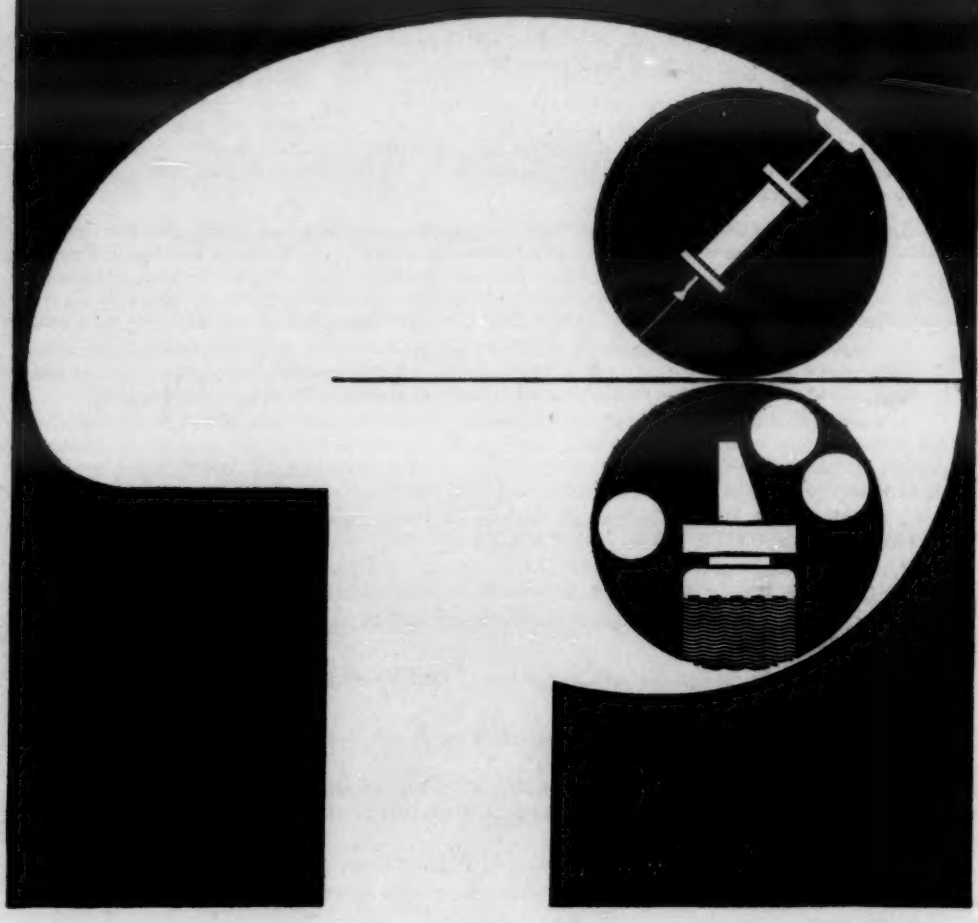

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